

OCCUPATIONAL RESPIRATORY DISEASES

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FOREWORD

Section 112 of the Black Lung Benefits Reform Act of 1977 mandated the Secretary of Labor, in cooperation with the National Institute for Occupational Safety and Health (NIOSH), to conduct a comprehensive study of all occupational respiratory diseases. It was suggested by the Senate amendment that the report be conducted in three phases: 1) Disease definition, etiology, and pathology; 2) Assessment of the adequacy of current workers' compensation programs; and 3) The status and adequacy of Federal health and safety laws and regulations relating to the industries with which such diseases are associated. The NIOSH contribution to this effort has focused on the first phase of the overall study and was facilitated by an interagency agreement with the Department of Labor.

The first part of this report delineates the methods used to define and study occupational respiratory diseases and addresses a host of broad topics such as assessment of chest X-rays, pulmonary function data, and lung impairment. Although these reviews are themselves valuable in understanding occupational lung diseases, their principal value is in allowing the reader to more fully understand the second part of this Report which deals with specific classes of these diseases—their definition, epidemiology, diagnosis, and treatment.

In compiling this report, we have been fortunate in having the cooperation and assistance of the Nations' experts on these various diseases. We have profited by the availability of a wealth of environmental data from the National Occupational Hazard Survey and other NIOSH epidemiological studies. We have also received strong support from several divisions within NIOSH.

It is clear from this report that occupational respiratory diseases are a potential threat across a broad range of industrial sectors. These diseases may be acute, but are often chronic. As a result they constitute the most important class of health effects arising from work place exposure. This report is published with the hope that it will contribute to our understanding of these diseases, their etiology, their diagnosis, and especially to their prevention.

James A. Merchant, M.D., Dr. P.H.
Editor

September 1981

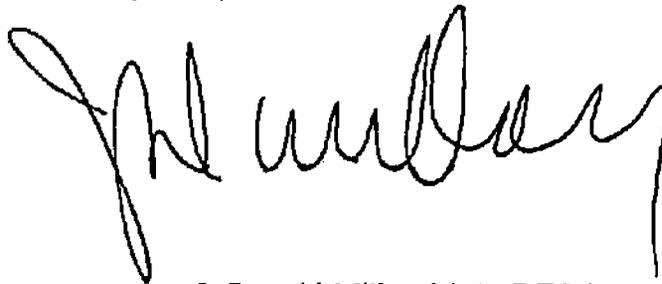
PREFACE

The National Institute for Occupational Safety and Health (NIOSH) is pleased to present this Occupational Respiratory Disease Report to the public. The information contained in this report should help all of us in reaching the United States Public Health Service 1990 Objective of a more healthful workplace.

The document seeks to describe the respiratory disease processes which affect the American worker, the requisite tools of evaluation, the existing methods of prevention, and areas where further effort and research are needed. We hope it provides a useful review of where we are today and where we need to go in order to eliminate the burden of occupational respiratory disease.

In a field expanding as rapidly as is research in occupational respiratory disease, new findings are reported daily. Thus, it is not possible always to incorporate the very latest information into reports such as this. Nonetheless, we present this book in hopes it will be a helpful, well-referenced treatise on occupational respiratory disease.

We sincerely appreciate the months of hard work devoted to this volume by the authors, reviewers, and editorial staff. Their diligent efforts should help all individuals who are concerned with the elimination of respiratory disease from the American workplace.

A handwritten signature in black ink, appearing to read "J. Donald Millar". The signature is fluid and cursive, with a large initial "J" and "M".

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**Appendix Table: The U.S. Population at
Risk to Occupational Respiratory Diseases**

Screening

Epidemiology

Beryllium Disease

Acute Systemic Effects of Inhaled
Occupational Agents

Pathology of Occupational Lung Cancer

Occupational Asthma and Rhinitis

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When you come to a patient's house, you should ask him what sort of pains he has, what caused them, how many days he has been ill, whether the bowels are working and what sort of food he eats. So says Hippocrates in his work Affections. I may venture to add one more question: what occupation does he follow? In medical practice, I find that attention is hardly ever paid to this matter, or if the doctor in attendance knows it without asking, he gives little heed to it, though for effective treatment evidence of this sort has the utmost weight...

...Preface to De Morbis Artificum by Bernardini Ramazzini (1770)

SECTION I
METHODS OF STUDY AND EVALUATION OF
OCCUPATIONAL RESPIRATORY DISEASES

CHARACTERIZATION AND MEASUREMENT OF THE INDUSTRIAL ENVIRONMENT

MINERALOGY

Arthur M. Langer

NATURAL AGENTS OF DISEASE

Exploitation of metal ores and fossil fuels, and the quarrying and mining of nonmetallic rocks and minerals, are carried out primarily on and within the earth's continental crust which extends from the tidal zones along the ocean margins of land masses to the mountainous highlands and interior "shields" of continents. The lithological units constituting the earth's surface may range from unconsolidated beach sands to dense, crystalline rock massifs which often form the "spines" of many of the great mountain ranges of the world.

Those who work in these environments may be exposed by inhalation to powders arising from fragmented or comminuted rocks, minerals, and ores. Miners, millers, stone masons, quarry men, tunnel drivers, to name but a few, may develop pneumoconiosis and, in some instances, malignant neoplasms as the result of such exposures. These diseases are also evident among working populations which process or handle such materials in secondary capacities, e.g., nickel ore millers and processors and nickel smelter workers, who develop lung and sinus cancers; workmen who use these substances in a variety of applications, such as insulation workers who handle asbestos fiber and who suffer the asbestos diseases; and foundry workers who use molding sands and who develop silicosis.

An appreciation of the nature of the crust, its rock types and ores, and its specific mineral prevalence, distribution, and association, is essential to any fundamental comprehension of the nature, extent, and distribution of dust-related diseases. This is especially important where agents of disease are known and have been identified.

THE EARTH'S CRUST

On the basis of geophysical, geochemical, mineralogical, and petrological data, much is known concerning the physical/chemical nature

of the crust. Geophysical data suggest its profile may extend from the surface down to a depth of some 60 km. It is thickest in continental regions where mountain building is still active. However, in other areas it may be thin, almost disappearing at the continent-ocean contacts. Variation and range in crustal depth are related to factors such as proximity to ocean basins or mountain ranges and location with "colliding" continental plates.

The concentration of exploited minerals and fossil fuels confines most human activities to the uppermost crust and surface. In some gold mining districts of the world, mine shafts with depths of four km. have been sunk. The depth limitations of these shafts are primarily due to the mine air temperature and humidity; the former may be near 50°C (because of the geothermal gradient) and the latter at 100% "wet bulb," due to evaporating ground water and water coolants used on the mine drift walls. Therefore, human activities (direct mining) are carried out in the crustal "veneer," with most mining and exploitation operations confined to the upper several thousand feet (approximately 2 km.).

COMPOSITION OF THE CRUST

An understanding of minerals found in the crust requires some basic information regarding their chemistry. The chemical composition of the crust is uniform on the large scale, with only some 8 elements constituting almost 99% of its mass (Table I-1a). It is from these few elements that the overwhelming majority of minerals are formed. The two most abundant elements are oxygen and silicon; hence we have prolific supplies of silicate minerals and silica polymorphs, especially quartz. The ore minerals, those from which we extract most metals, metalloids, and other substances, are frequently nonsilicates which contain the less common elements ordinarily distributed as trace quantities. These have been concentrated sufficiently, by specific

geological processes, to permit their exploitation as "ores." (Table I-1b).

The affinity of silicon for oxygen, together with its varietal bonding possibilities, results in many polymerization forms. This creates a variety of crystalline structures into which cations of differing species, size, and charge may fit. Six major structural types of silicate minerals result and the diversity of structural accommodations for differing cation species gives rise to the many silicate mineral forms that make up the earth's crust. The principles governing crystallization of minerals are outlined in the section on igneous rocks.

Table I-1a

CHEMISTRY OF THE EARTH'S CRUST
Major Elements Constituting the Crust

Element	Weight %	Atomic %	Volume %
Oxygen	46.6	62.6	93.8
Silicon	27.7	21.2	0.9
Aluminum	8.1	6.5	0.5
Iron	5.0	1.9	0.4
Calcium	3.6	1.9	1.0
Sodium	2.8	2.6	1.3
Potassium	2.6	1.4	1.8
Magnesium	2.1	1.8	0.3
	98.5	99.9	100.0

THE CLASSIFICATION OF
CRUSTAL ROCKS

The earth's crust is comprised of rock types, which appear to vary greatly in mineral composition and physical character. Three generic rock types are recognized, with varietal classes based on the mode of origin. These are:

Igneous rocks, which form primarily through the crystallization of molten magma on or beneath the earth's surface.

Sedimentary rocks, which form primarily through the accumulation of erosional debris; floral and faunal deposits; some forms of volcanic ejecta; and the chemical precipitates. These materials were derived from the degradation products of pre-existing rocks and through the accumulation of crustal organisms.

Metamorphic rocks, which form through the change of pre-existing lithological units by

recrystallization under superimposed new temperatures, pressures, and chemical processes. Mineral character is normally changed and textural relationships among minerals are altered.

Each rock type, in addition to its unique mode of formation normally possesses characteristic constituent minerals, structures, and textures. Each may act as a host for ore deposition. Some discussion of these characteristics will help define the nature and character of their mineral populations.

THE IGNEOUS ROCKS

Often considered "primary," igneous rocks (from the Latin stem *ignare*, meaning *fire*) are formed from the crystallization of molten magma, on or beneath the earth's surface. The resultant mineral species, and their textures (grain-size and geometric relationships) often reflect the parent magma and crystallization under specific conditions of temperature and pressure. The molten sources (magmas) of all igneous rocks are chemically referred to as silicate melts. Melts may vary in temperature and chemistry, kinds of cationic species present, amount of silica, water contents, etc. Such variation produces different end-product rocks and partly accounts for the observable igneous rock diversity.

Magmatic Crystallization

Magmatic melts may originate from numerous subcrustal zones, probably the lower crust or the earth's upper mantle, where pre-existing rocks are heated by a variety of processes. After heating, melts develop ductility and are transported by tectonic or volcanic forces to places where they undergo crystallization. Deep within the crust, the melt may begin to crystallize and the process of igneous rock formation begins. However, while working their way to the surface—and depending upon local conditions (e.g., host rock types)—such high temperature silicate melts may remelt and assimilate surrounding in-place host rock units. This may profoundly alter the composition of the original melt and will yield much different rock types upon crystallization. Hence, although basaltic magmas (considered "primary" magma) should only produce a few rock types, other confounding factors are operative which produce complex rock and mineral suites.

The crystallization of silicate melts begins

Table I-1b
CHEMISTRY OF THE EARTH'S CRUST
Minor and Trace Elements in the Crust (Concentration in Parts Per Million)

Element	PPM	Element	PPM	Element	PPM	Element	PPM
Titanium	4,400	Rubidium	120	Lanthanum	18	Mercury	0.5
Hydrogen	1,400	Vanadium	110	Lead	15	Antimony	0.2
Phosphorus	1,180	Nickel	80	Gallium	15	Bismuth	0.2
Manganese	1,000	Zinc	65	Thorium	10	Cadmium	0.2
Sulphur	520	Nitrogen	46	Scandium	5	Silver	0.1
Fluorine	500	Cesium	46	Tin	3	Platinum	0.005
Strontium	450	Copper	45	Bromine	3	Gold	0.005
Barium	400	Yttrium	40	Beryllium	3	All others	
Carbon	320	Lithium	30	Arsenic	2	<0.005	
Chlorine	200	Neodymium	24	Uranium	2	(5 ppb)	
Chromium	200	Niobium	24	Tungsten	1		
Zirconium	160	Cobalt	23	Molybdenum	1		

in the molten state, as evidenced by recent studies of volcanic glasses (quenched melts) which demonstrate that crystalline domains (ordering) of silicon and oxygen and aluminum and oxygen, take place in materials which have been previously considered "glassy" (amorphous). Normally, the silicon-oxygen polymerization begins as silicon and oxygen complexes so that "bridging" increases, producing a progressive ordering of structure and a more stable thermodynamic unit.

As crystallization of a silicate melt proceeds, a number of chemical bridging events occur: single, isolated silica tetrahedra exist, forming structures only when joined together by cations; as temperature decreases, tetrahedra may share a corner oxygen to form double tetrahedral structures and eventually single infinite chains; with further temperature decreases, shared corners of silica tetrahedra form "double chains"; additional corner sharing of silica tetrahedra produces a two dimensional structure called a "sheet"; finally, the complete sharing of all tetrahedral apices forms a three-dimensional framework structure. During this process, the silicon to aluminum ratio decreases, the alkalis within the melt increase, the water and volatile contents of the melt increase, the fluorine and chlorine content of minerals increase, the unit cell volumes of the mineral species increase, and the mineral densities decrease (see Table I-2).

These chemical trends reflect the chemical properties of the different atomic species in the melt. Included, as some of the important properties, are ionic radius, valence state, and electronegativity.

The first silicate mineral to crystallize is olivine. This phase then reacts with the melt (in which it has just crystallized) to form pyroxene. Pyroxene subsequently reacts to form amphiboles, and the amphiboles react to form micas. These reactions need not proceed to completion; consequently "survivor minerals" of the crystallization process are frequently observed in a variety of igneous rocks. Several mineral series may crystallize simultaneously (Table I-2). In addition to the ferromagnesium series, the feldspars crystallize at the same time. The calcium-aluminum varieties predominate at first, then change to the sodium varieties and end with those that are potassium rich. The potassic feldspars crystallize normally with the mineral quartz; the mica variety muscovite may end with zeolite and other "hydrothermal minerals."

Crystallization follows physical-chemical laws, one of which (the "phase-rule") implies that only a limited range of mineral phases may form at any one time. Almost 99% of the mineral composition of igneous rocks may be represented by 5 mineral groups and the silica phase quartz. The mineral groups and the common

Table I-2
PHYSICAL-CHEMICAL CHANGES ACCOMPANYING THE
CRYSTALLIZATION OF BASALTIC MAGMA

Temperature of Melt During Crystallization

High temperature (~1250°C) —————> Low temperature (~750°)

Major Cations Incorporated in Minerals During Crystallization

Mg > Fe —————> Fe ≅ Mg —————> Fe ≫ Mg
 Ca ≫ Na, K —————> Na, K ≅ Ca —————> K > Na ≫ Ca
 Si ≅ Al —————> (variable) —————> Si > Al
 -H₂O (anhydrous) —————> + H₂O (hydrous)
 -Volatiles —————> + Volatiles (F, Cl, B)

Polymerization of Silicon and Oxygen and Representative Minerals:

SiO ₄	—————>	SiO ₃	—————>	Si ₂ O ₇	—————>	Si ₂ O ₅	—————>	SiO ₂
nesosilicates		inosilicates		inosilicates		phyllosilicates		tektosilicates
(isolated tetrahedra)		(single chain)		(double chain)		(sheets)		(3-dimensional framework)
olivine(s)		pyroxene(s)		amphibole(s)		mica(s)		feldspar(s)

Physical Changes in Minerals

High density minerals —————> Low density minerals
 Small unit cell dimensions —————> Large unit cell dimensions

Mineral Crystallization Sequences

Ferromagnesian:

Olivine —————> Pyroxene —————> Amphiboles —————> Mica

Feldspars:

Ca > Na Plagioclase > Potassic —————> Potassic > Na > Ca

Quartz:

None or little —————> Quartz-rich

Rock-type and Crystallization

Gabbro (intrusive)	—————>	Intermediate	—————>	Granite (intrusive)
↓	—————>	—————>	—————>	—————>
Basalt (extrusive)	—————>	Andesite	—————>	Rhyolite (extrusive)
			some	
			some	

←————— Serpentine deposits —————> Quartz-rich

←————— Talc deposits

representative species within them are given in Tables I-3—I-8.

Rock-Forming Silicates

Often rock-forming silicates are described on the basis of their chemistry. Commonly, they are mixtures of different cationic species which substitute within the basic structure formed by bridged oxygen and silicon atoms. "Pure" mineral species, those made of single constituent cations, are rare. Rock-forming silicates tend to be composed of "solid-solutions" of representative end-member species. These end-members are also rarely found in nature and are in many instances hypothetical—used for chemical convenience. For example, the olivine minerals forsterite and fayalite, (Table I-3), are rarely observed in nature. Divalent iron and magnesium readily substitute for each other within silicate minerals, on the basis of their ionic radii, valence, and electronegativity. Therefore, most species of olivine consist of "mixtures" of the end-members, forsterite and fayalite. This concept may be carried forth to the pyroxene minerals (Table I-4) which are considered mixtures of wollastonite, enstatite, and ferrosilite; the amphibole minerals (Table I-5) which are further subdivided into a number of end-member groups, e.g., cummingtonite-grunerite, tremolite-actinolite, etc.; feldspars (Table I-6) e.g., the plagioclase series, albite-anorthite; and the rock-forming micas (Table I-7), with structural substitution based primarily on cationic charge in the octahedral structural layer.

Therefore, the crystallization of silicate melts produces a number of mineral species with specific structures and chemical constituents. Despite their large mineral diversity, these materials—the products of magmatic crystallization—produce only a limited number of mineral species. The average mineral content of crustal igneous rocks tends to be relatively small, yet varying proportions produce the varietal rock types (see Table I-9).

Crystallization and Trace Metals

The principles of crystal chemistry also apply for trace elements. Elemental coordination number or geometrical factors (the radius ratio

Table I-3
CRYSTAL CHEMISTRY OF THE
ROCK-FORMING OLIVINE MINERALS

Empirical Formula: X_2SiO_4

X = divalent cations, $Fe^{+2}, Mg^{+2}, Ca^{+2}$
if $Mg = Mg_2SiO_4$ = forsterite
if $Fe = Fe_2SiO_4$ = fayalite

Pure Mg,Fe phases are uncommon

Most olivines are "mixtures" of Fe and Mg, expressed as mole percent Forsterite (Fo), Fayalite (Fa), e.g., olivine ($Fo_{80}Fa_{20}$)

Olivine is readily altered at and near the earth's surface to the serpentine minerals.

effect) and electrical satisfaction (valence) together control distribution of trace metals in the minerals of igneous rock types. For example, on the basis of valence and size: nickel and cobalt occur in iron-magnesium minerals; strontium occurs in calcium minerals; rubidium occurs in potassium minerals; germanium occurs in silica minerals; gallium occurs in aluminum minerals. Therefore, one would anticipate concentrations of nickel in mafic rocks (high in ferromagnesian minerals) and concentrations of rubidium in potassic rich rocks (e.g., granitic in composition).

Classification of Igneous Rock by Mode of Occurrence and Resultant Texture

There are two broad categories of igneous rocks. *Intrusive* (plutonic) igneous rocks are those which form beneath the earth's surface; *extrusive* igneous rocks are those which form on or near the surface. In plutonic (intrusive) rocks, the magmatic crystallization is slow and individual mineral components grow to large dimensions, clearly visible to the unaided eye. Such is the case for intrusive (plutonic) rocks. On the other hand, those igneous rocks which form at the surface undergo rapid crystallization. The resulting mineral texture is *fine-grained*, so that individual mineral components are not visible to the naked eye.

Magma of identical composition may form physically different rock-types based on mineral size (texture). Magma of basaltic composition, crystallizing beneath the surface, may form a coarse-grained rock which would be termed a gabbro; the same magma crystallizing on the surface would form a fine-grained equivalent termed a basalt (Table I-10).

By Outcrop Size and Relationship to Host Rock

In addition to textural characteristics, igneous rocks may be further classified according to outcrop dimension. Large mountain complexes (usually granite or granodiorite) are called batholiths. A mineralogically identical intrusive igneous body of smaller dimension may be termed a stock. In these cases, the field term would be modified by rock-type term. Also, the relationship of the intrusive with the surrounding host rock may determine nomenclature, e.g., if the igneous body conforms with the local structure, it may be termed a sill; if it is discordant, it may be termed a dike. These terms are frequently encountered in the mining literature.

By Mineral Content (Composition)

Lastly, igneous rocks are classified on the basis of their mineral content. The final products of crystallization reflect, in essence, the chemistry of the melt. Specific mineral species produce specific rock types. For example, granite is commonly composed of potassic feldspars, minor amounts of sodic feldspars, quartz, and possibly some mica (either muscovite or biotite). Occasionally, amphibole minerals may occur as well. Gabbroic rocks contain feldspars which are calcic, pyroxenes, and occasionally olivine minerals. They normally do not contain quartz, micas, or amphiboles. These mineral suites are generalizations (see Table I-2, I-10).

The reader will likely be familiar with some names of common igneous rocks in Table I-10. It should be noted that granites and granodiorites, common plutonic rocks, tend to be quartz-poor.* The rocks named in Table I-10 range from varieties containing potassium, sodium, and calcium to those which contain high

*Silicosis is more prevalent in workers exposed to dusts generated from the granite-type lithologies; silicosis is almost never seen in workers exposed to dusts generated from basalts.

concentrations of iron and magnesium.

THE SEDIMENTARY ROCKS

Sedimentary rock types originate through a multitude of processes, which occur at or near the earth's surface, and under conditions normal to the earth's surface (relatively low temperatures and pressures). Pre-existing crystalline rocks, those of igneous and metamorphic origins, are basically unstable under conditions at the earth's surface. Because these were formed under high temperatures and pressures, their mineral components succumb easily to the chemical action of water, surface- and atmospheric-formed acids, and oxygen. Lithologies attacked in this manner may be further subjected to degradation through the mechanical effects of moving air and water in all its forms. The processes of physical-chemical weathering, erosion, transport, deposition, and diagenesis act in concert to create new rock types.

There have been a number of systems proposed for the classification of sedimentary rocks. All reflect the precursor material, the mode of formation, and other factors. Sedimentary rocks tend to be more varied and complex than other rock types: they arise from the products of erosion as diverse as the crust itself. There are two broad classes of sedimentary rocks:

1. The *Clastics* include mechanically deposited erosional debris from pre-existing surface lithologic units and in some instances, deposits of volcanic ejecta. Clastic rocks originate through the accumulation of single, discrete particulate debris, mechanically deposited as unconsolidated sediments. Most accumulation of nonclay-sized particles is brought about by settling processes, as the result of transport failure.
2. *Chemical precipitates* include rocks or materials formed through physical-chemical and organic processes (which account for the accumulation of mineral matter). The chemical precipitates include the carbonate lithologies (a major rock type on the crust of the earth), shells and hard parts of organism skeletons (for example, diatoms, coral, etc.), and saline deposits (which include evaporites and hot springs). These latter rock types form through chemical processes, mostly in water involved reactions, and are re-

Table I-4
CRYSTAL CHEMISTRY OF THE ROCK-FORMING PYROXENE MINERALS

Empirical Formula: $XY(ZO_3)_2 = Z_2O_6$
 $X = Ca, Mg, Fe, Li, Mn, Na$
 $Y = Fe^{+3}, Fe^{+2}, Mg, Al$
 $Z = Al, Si$

Common pyroxene minerals are defined by mole percents of the phases: CaSiO₃, [Wollastonite (Wo)], MgSiO₃, [Enstatite (En)], FeSiO₃, [Ferrosilite (Fs)]

Orthorhombic pyroxenes:

Enstatite, MgSiO₃, (En ≧ Fs), ± TrWo
 Hypersthene, (MgFe) SiO₃, (En > Fs), ± TrWo

Monoclinic pyroxenes:

Diopside CaMgSi₂O₆, (Wo, En > Fs)
 Hedenbergite CaFeSi₂O₆, (Wo, Fs > En)
 Augite (Series between diopside and hedenbergite as end-members)
 Pigeonite (En Fs*Wo; calcium-rich E-Hy)
 Aegerine NaFe⁺³Si₂O₆
 Jadeite NaAlSi₂O₆
 Spodumene LiAlSi₂O₆

—Al-rich varieties tend to originate under high-pressure conditions. XY positions acquire a plus (+) four charge. If Al⁺³ occupies the Y site, then a monovalent cation occupies the X site.

Table I-5
CRYSTAL CHEMISTRY OF THE ROCK-FORMING AMPHIBOLE MINERALS

Empirical Formula: $W_{0-1}X_2Y_3(Z_4O_{11})_2(O, OH, F)_2$
 $W = Ca, Na, K$ as trace or minor element.
 $X = Ca, Mg, Fe^{2+}, Mn$
 $Y = Fe^{2+}, Mg, Ti, Al, Fe^{3+}$
 $Z = Si, Al$

As with pyroxenes, minerals may be expressed as mole percents of end-members

Orthorhombic amphiboles

Anthophyllite (MgFe)₇Si₈O₂₂(OH)₂NoCa
 $W = O; X, Y = Mg, Fe (Mg \geq 6); Z = Xi, TrAl$
 Gedrite (MgFe)₃(AlSi)₄O₂₂(OH)₂NoCa
 $W = O, X, Y = MgFe (Mg \geq 6); Z = Al, Si$

Monoclinic amphiboles

Cummingtonite-grunerite series (Mg→Fe), NoCa
 $W = O; X, Y = Mg, Fe; Z = Si$
 Tremolite-actinolite series Ca₂(Mg→Fe)₅; High Ca
 $W = O, X = Ca; Y = Mg, Fe; Z = Si$
 Hornblende series High Ca
 $W = 0-1, Na_{0-1}, K; X = Ca; Y = Mg, Fe, Al; Z = Al, Si$
 Alkali amphibole series Na = 2 High Na
 $W = O; X = Na; X, Y = Mg, Fe, Al; Z = Si$

e.g., Glaucophanes = Na₂Mg₃Al₁(Si₄O₁₁)₂(OH)₂
 Riebeckite = Na₂Fe²⁺Fe³⁺(Si₄O₁₁)₂(OH)₂

Table I-6
CRYSTAL CHEMISTRY OF ROCK-FORMING FELDSPARS

Empirical Formula: WZ_2O_6

W = Na, K, Ca, Ba

Z = Al, Si

Feldspars are generally grouped as two separate series on the basis of: major cation, structure, and geological occurrence.

Plagioclase: Solid solution series between anorthite ($CaAl_2Si_2O_8$) = An and albite ($Na_2Al_2Si_2O_8$) = Ab [produces 6 feldspars; all triclinic]

anorthite	An \geq 90 Ab \leq 10
bytownite	An 89-70
labradorite	An 69-50
andesite	An 49-30
oligoclase	An 29-10
albite	An \leq 9 Ab \geq 91

“Orthoclase group” commonly called K-spar or alkali series:

	$KAlSi_3O_8$ - All but microcline = <i>monoclinic</i>
sanidine:	monoclinic, high T, volcanic rocks
orthoclase:	mono, high T, plutonic rocks
microcline:	triclinic, low T, pegmatite rocks
adularia:	monoclinic, low T, authigenic origin
anorthoclase (Na):	triclinic, high T, volcanic rocks
celsian (Ba):	monoclinic, high T, volcanic rocks

Table I-7
CRYSTAL CHEMISTRY OF THE ROCK-FORMING MICAS

Empirical Formula: $W(X, Y)_{2-3} Z_4O_{10} (O, OH, F)_2$

W = K, Na

X, Y = Al, Li, Mg, Fe²⁺³

Z = Si, Al (3:1)

Micas are grouped according to number of sites filled in their octahedral layers (total charge per cell is ⁻⁶). If divalent cations occupy the site, then *three* are required to satisfy the valency, hence the micas are *trioctahedral*; if trivalent cations, *two* are required, hence, the micas are *dioctahedral*.

Dioctahedral	Muscovite	$KAl_2(AlSi_3O_{10})(OH)_2$
	Paragonite	$NaAl_2(AlSi_3O_{10})(OH)_2$
	Lepidolite	$KLi_2Al(Si_4O_{10})(OH)_2$
Trioctahedral	Biotite	$K(MgFe)_3(AlSi_3O_{10})(OH)_2$
	Phlogopite	$KMg_3(AlSi_3O_{10})(OH)_2$

Table I-8
CRYSTAL CHEMISTRY OF THE ROCK-FORMING SILICA POLYMORPHS

Empirical Formula: XO_2		
	$X=Si$	
Quartz	SiO_2	Common
Cristobalite	SiO_2	Uncommon
Tridymite	SiO_2	Uncommon
Coesite	SiO_2	Rare: High pressure phase
Stishovite	SiO_2	Rare: High pressure phase
Opal	SiO_2	n H_2O : Major form of biogenic silica
"Amorphous" silica (SiO_2): X-ray amorphous—common		

Other forms of silica exist in nature: e.g., silica glasses, (fulgurite). Silica phases exist as low- and high-temperature enantiomorphs and may occur with racemic varieties as well (quartz).

lated to environmental physical-chemical factors such as pH, ionization potential of constituent ions, reduction-oxidation potentials of elemental constituents, etc. Commonly, sedimentary rocks are composed of mixtures of rock-types, e.g., sandy limestones or calcareous sandstones.

Erosion

Exposed pre-existing rock units at the surface of the earth are subjected to erosion by a number of processes and forces: moving water (streams, wave action, glacial ice, underground waters); moving air; atmospheric radiation (heat fluctuation producing expansion and contraction of rocks); frost shattering; plant wedging; earthquake and volcanic forces; chemical weathering (oxidation, hydration, and hydrolysis); and atmospheric and organic acid attacks. These mechanisms attack component minerals and physically and chemically break down rocks. The resulting debris (single minerals, rock fragments, dissolved salts) may then be transported to another location where deposition occurs. The physical process of tumbling, saltation, particle impaction, abrasion rubbing, etc., tend to produce a general size reduction and "rounding" of debris constituents when particulates are transported in water.

The capacity of moving water to carry these erosional products is enormous, increasing exponentially as the velocity of the fluid doubles. Water volume, stream gradient (which determines velocity), nature of source debris, and

physical-chemical character of water (temperature, pH, etc.) determine the amount of sediment transported, the degree of alteration of the carried debris, and the ultimate distance it is carried from the source material.

Erosion is a complex process involving interface between the atmosphere, the hydrosphere, and the rocks of the earth's crust. Erosion may be related to such large scale factors as climate (influencing both mean and extreme temperatures, rainfall), flora and fauna, mean elevation above sea level, and local topographic factors (especially slope), to name but a few. These general factors, considered in perspective with erosional processes, may produce vastly different degradation products originating from the same host rock.

A good example of complex factors in erosion can be illustrated by the physical-chemical degradation of limestone (calcium carbonate, $CaCO_3$). A limestone undergoing erosion in a wet, mountainous, hot climate would be readily affected by: rain acidified by atmospheric carbon dioxide (forming carbonic acid); the bicarbonate phase, which is some thirty times more soluble at the same temperature, pH, and volume of solute than the carbonate phase; high temperatures which would greatly enhance chemical reaction kinetics (the activity of some chemical reactions may double with increases of approximately $10^\circ C$); growth of flora and fauna which would increase the mechanical work of plant root systems into the carbonate soil and bedrock, increasing a *wedging effect*; the proliferation of soil organisms in the tropical environment which

Table I-9
AVERAGE MINERAL CONTENT OF CRUSTAL IGNEOUS ROCKS*

Mineral Species	% Occurrence (by weight)
Quartz (Silica)	12.0
Feldspars (K,Na,Ca)	59.5
Ferromagnesian minerals (amphiboles and pyroxenes)	16.8
Biotite (Mica)	3.8
"Ores" (sulfides, oxides)	1.5
Apatite	0.6
"Others" (including micas and clays)	5.8

*Based on an average of mineralogically characterized units cropping out on the continental surface.
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can alter pH conditions of the soil and greatly increase acidity; and the mountainous topography (steep slopes) which can increase the activity of running water, its capacity for transporting sediment, its mechanical energy for erosion and transport, etc. Limestone will succumb under this condition readily. Yet, the same limestone existing under dry desert conditions would be essentially impervious to attack—as evidenced by the survival of the Egyptian pyramids, the bases of which are built entirely of limestone.

In addition to environmental factors, the chemistry of the rock type, the texture of the composite grains (spacial interrelationships), and structural characteristics (jointing, cleating, superimposed fissility) etc., have profound effects on erosion.

Deposition

The transport of sediment in a moving stream may end with deposition of clastic objects in accordance with their sizes and specific gravities. This may result in a form of "sorting." Major factors in such transport failure are reduction in stream velocity (gradient related) or reduction in water volume. Essentially, large heavy objects settle out first, followed by those of decreasing size and density. Clay particles of colloidal size settle out last. Normally, because of Brownian Motion, special conditions are required for clay settling, including slowing of water velocity to essentially zero, lowering of temperature to almost freezing (slowing the thermal motion of water molecules), and change in salinity (effecting cation concentration and thickness of the sorbed water layers on the particle's surface), etc. These processes may induce clay settling so that gravitational forces may overcome interpar-

ticle repulsion which maintains the particles in suspension.

If, after deposition, the clastic materials are well sorted (sizes fall within a narrow range), the nomenclature of rock-type is based on size rather than composition.

Minerals Constituting Clastic Particle Populations

The rock-forming silicate minerals succumb to weathering and erosional processes differently. Physical degradation of minerals may be related to such factors as cleavage, controlled by both its molecular structure and atomic species. Minerals with "good" or "excellent" cleavage tend to disappear in the environment more easily than minerals with "poor" or "no" cleavage. Chemical degradation of minerals is related to other factors, such as surface hydrolysis of cations. Based on a study of particle populations in sediments, it was observed that high temperature mineral species tend to succumb first during erosion and transportation (Table I-11). Mineral stability appeared to be the reverse of Bowen's crystallization series for igneous rocks. Minerals which crystallize first (e.g., olivine, pyroxene, etc.) are rare components of detrital sediments. Their prevalence in the environment is dependent upon these broadly related factors. Mineral survivor populations consist primarily of quartz, the potash feldspars, and muscovite. These form such rock types as sandstones, arkoses, siltstones, etc. (see Table I-11). Considering all rock types at the earth's surface (igneous, metamorphic, and pre-existing sedimentary units), mineral survival is well established (Table I-12).

Regardless of the mineral character, sedimentary rocks may be classified merely on the

Table I-10
COMMON IGNEOUS ROCKS

Intrusive (Plutonic)		Extrusive (Volcanic)	
Individual mineral grains visible to unaided eye (phaneritic)		Individual mineral grains invisible to unaided eye (aphanitic)	
SiO ₂ : Saturated (+ Quartz)	SiO ₂ : Undersaturated (- Quartz)	SiO ₂ : Saturated (+ Quartz)	SiO ₂ : Undersaturated (- Quartz)
<i>Acidic or Felsic</i>			
Granite	Syenite	Rhyolite	Trachyte
Granodiorite	Diorite	Quartz Latite	
Tonalite	Diabase	Dacite	Andesite
Quartz Gabbro	Gabbro	Tholeiitic Basalt	Olivine Basalt
<i>Basic or Mafic</i>			
	<i>Ultramafic</i>		
	Peridotite		
	Dunite		
Other Common rock-types:			
Volcanic tuffs, breccias, agglomerates (these are textural terms other than compositional), volcanic glasses including obsidian, pitchstone, perlite, pumice, etc.			

basis of the particle size of the component grains (Table I-13). Large rock fragments form "gravels" (sizes greater than 256 mm) and when indurated, form rock types called "conglomerates," "breccias," "tillites," etc. Depending on the angularity of the components, their sources, etc., nomenclature may change (See Table I-13). Basically, very fine particles form sedimentary rocks called "shale," "siltstone," "mudstone," or "argillite." Sand-size grains form "sandstones," "arkoses," and "graywackes." Occasionally modifying terms may be used to indicate deposition in a standing body of water, a moving body of water, from volcanic ejecta, etc.

The above rock types may be further modified by mixtures, so that a silt-containing sandstone may be referred to as "silty/sandstone." It is also important to note that the composition of the particles may vary enormously. "Sand" sized particles may be quartz, feldspar, magnetite, garnet, ilmenite, or other minerals—reflecting different geological provenance, climate, transport and depositional history. Rock classification generally reflects size of components, not composition; yet the most common sandstone is composed of the mineral quartz.

The grain particles are considered "frameworks" which require an additional process or

bonding agent to "hold them together." This general process is called "lithification" and is the result of consolidation, compaction, dewatering, cementation, and recrystallization. Clastic sediments are dewatered (if waterborne in origin) by overburden compaction; they then lose pore space, undergo reorientation of grains, and retain introduced substances which precipitate and/or crystallize in the interparticle voids to form an intergranular cement. Occasionally, sediments may begin some form of recrystallization.

In essence, sedimentary clastic rocks are classified on the basis of *texture* (particle size and shape) and *composition* of composite grains (and cementing agent if present). Texture determines major rock type name, e.g., sandstone, shale, etc. Structures of sedimentary clastic rock may include ripple marks, layering (stratification), mud cracks, etc. The variation in sedimentary rock nomenclature is also given in Table I-13.

The Chemically Precipitated Sedimentary Rocks

The process of weathering (the major process involved in the formation of precursor material for sedimentary rocks) is basically chemical. Although physical weathering pro-

Table I-11
GOLDRICH'S STABILITY SERIES
(RESISTANCE TO PHYSICAL-CHEMICAL WEATHERING)

Most resistant:

Quartz
 Muscovite
 Potash feldspars
 Biotite = alkalic feldspars
 Hornblende = alkalic-calcic plagioclase
 Calcic-alkalic plagioclase
 Augite (pyroxenes) = calcic plagioclase
 Olivine

Deposited as survivor minerals to form sandstones, arkoses, siltstones, etc.

Least resistant:

At or near surface succumbs to attack. Tends to form serpentines when subjected to hydrothermal attack in upper crust.

Granites and sandstones are more durable at the earth's surface than gabbros and basalts. Conversely, ultramafic and mafic rocks containing magnesium silicate minerals tend to become serpentized during degradation.

cesses (such as freezing and thawing of ice in joints and rock fractures) may be locally important, chemical weathering is universal. Surface rocks in contact with the earth's atmosphere expose minerals with unsatisfied surface valencies to the chemical components of the atmosphere. These mineral surfaces may react with atmospheric moisture with resultant surface hydration and hydrolysis. Cations such as calcium, magnesium, and potassium are removed as soluble hydroxides in the weathering process. The processes of degradation and erosion are essentially chemical as well. It is only climate which determines reaction kinetics. The major chemically derived sedimentary rocks are given in Table I-14.

Chemistry and Mineralogy of Sedimentary Rock

The weathering of silicate minerals at the earth's crust and their subsequent erosion, removal, and deposition is largely controlled by chemical processes. Both chemical and physical degradation of pre-existing rocks produce sediments rich in quartz and feldspar and poor in olivine and pyroxene. Chemical breakdown also produces carbonates, the most common mineral form being calcite (CaCO₃). Under crustal conditions, almost all varieties of clays

Table I-12
MINERALS COMMONLY OBSERVED
IN DETRITAL SEDIMENTS

Very Common

Quartz
 Feldspar
 (K,Na,Ca)
 Muscovite
 Chlorite
 Biotite
 Apatite
 Hornblende
 Zircon

Common

Andalusite
 Augite and other
 pyroxenes
 Epidote
 Garnet
 Rutile
 Sphene
 Staurolite
 Tourmaline
 Zoisite
 Calcite

Formation of detrital sediments includes high concentrations of quartz.

result from chemical weathering, with structural reorganization of pre-existing minerals. For example, chemical degradation of mica may produce a hydromica and then illite clay.

The importance of chemical processes has often been illustrated by the fact that the products of erosion and surface weathering form

Table I-13
NOMENCLATURE OF CLASTIC SEDIMENTARY ROCKS:*
RELATIONSHIP OF PARTICLE COMMON NAME, PARTICLE SIZE AND SHAPE
(TEXTURE), AND ORIGIN OF DETRITUS

Components	Size Range (mm)	Grabau Size-classification	Indurated Lithological Units Based on Shape and Composition			Common Rock Names**
			Rounded	Angular	Volcanic	
Boulder (gravel)	≤ 256	Rudite	Conglomerate	Blocks	Bomb	Gravel, Till, Tillite, Talus, and others (specific instances)
Cobble (gravel)	256-64	Rudite	Conglomerate	Rubble Breccia	Bomb	Conglomerate Breccia
Pebble (gravel)	64-2	Rudite	Sandy Conglomerate	Rubble Breccia	Lapilli	Conglomerate Breccia
Sand	2-1/16	Arenite	Sandstone	Grit	Coarse Ash	Sandstone, Arkose, Graywacke Tuff
Silt	6/16-1/256	Arenite Lutite	Siltstone	Grit	Coarse Ash Fine Ash	Siltstone, Ignimbrite Ash
Clay	≤ 1/256	Lutite	Shale	—	Fine Ash	Shale, Argillite, Limestone

*Represents a general classification: see classification schemes, discussion of relationships in Pettijohn, 1957, p. 225 ff.

**Rock names may be modified by compositional terms, reflecting either component grains or cementing agent.

sedimentary deposits which may be generally characterized as chemical residues (Table I-15). Sedimentary deposits may be characterized on a chemical basis as follows: *Resistates* are deposits in which the minerals have resisted chemical degradation and are mechanically manipulated without loss of mineral character. Quartz and potash feldspars are good examples. These minerals tend to form sandstones, pebbles in conglomerates, and also rocks known as arkoses. *Hydrolysates* are deposits in which minerals are formed which contain aluminum and silicon. Basically, they are aluminosilicates or clays. Cations in the unsatisfied valencies at the mineral surface are removed from the mineral through hydrolysis to form cation-hydrate complexes, which recombine with hydrolyzed silica to form the clay minerals. These new clays form rocks such as shales. *Oxidates* are deposits which originate through oxidation reactions. Some cationic

species are sensitive to slight variations in local pH conditions and may rapidly precipitate as oxide-hydroxide forms when specific chemical conditions have been met. These materials form important deposits of iron and manganese (banded iron-stones). *Carbonates* are deposits in which mineral salts containing carbonate or bicarbonate forms precipitate. Calcium carbonate is the dominant rock-type produced. Dolomites appear to be chemically modified calcium carbonate units, formed throughout the secondary introduction of magnesium-rich solutions. This accounts for a major sedimentary lithologic unit. *Evaporites* are deposits of salt minerals formed principally as a consequence of the concentration and precipitation which occurs through loss of solvent (water). A number of alkaline metals and earths—especially sodium, potassium, magnesium—concentrate in solution with halogens and complex anionic bases. Sulfates,

borates, and chloride and bromide compounds form many evaporite deposits, when their concentrations exceed their solubilities. Salt deposits of various kinds are formed in this manner. *Reduzates* are deposits formed as the result of reducing environments. Fossil fuels—coal and petroleum—constitute the bulk of these materials.

Sulfur, phosphorous, and organic compounds with trace metals in a range of forms, accumulate in these deposits.

Amounts and Kinds of Sediments in the Crust

Sedimentary rocks constitute only about 5% of the volume of the earth's crust. However, some 75% of the total land surface area is covered with such materials. Therefore, most of the outer veneer of the earth's crust is of sedimentary rock. Of this material, three common varieties constitute almost 99% of all sedimentary rocks. These are shale, sandstone, and limestone in that approximate order of abundance (Table I-16). It is of great importance to note that the average mineral content of the three most common sedimentary rocks consists of the most stable minerals in the Goldich Stability Series. Quartz, feldspar, and fine mica (sericite) constitute the bulk of shales and sandstones. For all the sedimentary rocks, only five mineral groups make up over 90% of the bulk material (Table I-17). If the average mineral composition

Table I-14

MAJOR CHEMICALLY PRECIPITATED SEDIMENTARY ROCKS

Limestones (predominately CaCO_3 with trace silicates)
Dolomites (predominately $\text{CaMg}(\text{CO}_3)_2$ with trace silicates)
Bioherms (accumulated shells)
Coquinal limestones (accumulated shells)
Cherts, flints, and other cryptocrystalline silica precipitates (normally in another host, especially limestones)
Diatomaceous earth, radiolarian cherts and related organic derived precipitates
Phosphorite deposits (trace radioactive components)
Iron formations (predominately iron oxides, hydroxides, and silica)
Coal and similar fossil fuel deposits (Not chemically precipitated— <i>sensu stricto</i>)
Salines and evaporite deposits
Sulfur deposits (through bacterial action on sulfate precursors)

It is currently accepted that some metal-sulfide ore deposits may have originated through bacterial action. These are not included in the above list.

Table I-15

CHEMICAL CLASSIFICATION OF SEDIMENTS (Based on Goldschmidt's Classification)

Group	Resistates	Hydrolysates	Oxidates	Carbonates	Evaporates	Reduzates
Major elements and compounds:	Si	Al, Si(K)* Hydrolyzed bases	$\text{Fe}(\text{OH})_3, \text{Fe}$	$\text{Ca}(\text{Mg})^*$ Carbonate Precipitates	$(\text{Ca})(\text{K})(\text{Mg})^*$ Na Chlorides, sulphates, etc.	$\text{C}, \text{Fe}^{+2}, \text{Mn}^{+2}$ Heavy metals
Minerals:	Quartz Feldspars	Clay minerals	Minor clays	CaCO_3 $\text{CaMgCO}_3)_2$	NaCl MgCl ₂	
Major Rock-types:	Sandstones Arkoses Siltstones	Shales	Iron-rich Sediments Shales	Limestones Dolomites	Saline Deposits	Fossil Fuels

*May be present in substantial quantities.

of crustal igneous rocks was compared with the average mineral content of crustal sedimentary rocks, one would see striking similarities. For example, based on six major oxide components of sedimentary and igneous rocks, the chemistry of the "average igneous rock" almost superimposes on the point of the "average crustal sedimentary shale"; the average composition of basaltic igneous rocks superimposes on the average chemical composition of carbonate rocks. Sedimentary rocks unacted upon by secondary geological processes are often "chemically fractionated" crystalline rocks.

METAMORPHIC ROCKS

Crustal processes, at temperatures and pressures in excess of those encountered in diagenesis and in association with altered chemical environments, may induce both physical and chemical changes in pre-existing rocks. These changes include recrystallization of mineral components, alteration of existing textures, and either introduction or removal of chemical constituents. These may occur in the solid state or, at elevated temperatures, include partial melting *in situ*. In the lower crust, where elevated temperature and pressures reach those encountered in the igneous regime, processes tend to merge so that these metamorphic products resemble igneous crystallization products.

The process of lithification of sedimentary rocks occurs post-depositionally. It involves formation of sedimentary rocks in indurated forms from previously loose and unconsolidated sediments. For example, during burial in a body of water, compaction, dewatering, reorientation of clays and other component grains, and subsequent cementation and partial recrystallization of components takes place. Further change in mineral texture or composition may rightfully be called metamorphism. In almost all cases, elevated temperatures and pressures are required for metamorphism. In orogenic belts, where tectonic forces are active, crustal movement along fault zones may induce changes in pre-existing lithological units through directed pressure. In areas of igneous activity, metamorphism may result through the effects of elevated contact temperatures. Usually, at the contact of igneous intrusions, elements may be mobilized and introduced to the host rock producing new mineral phases. Fluids escaping from such intrusions act as a medium to speed reactions. Water, carbon

dioxide, acids of boron, chlorine, and fluorine, may also promote kinetics.

Each rock type responds to produce a range of new products. Under the influence of elevated temperatures, pressures, and fluids, the final product of a metamorphic process is an assemblage of minerals reflecting the original material and the superimposed environmental condition. Single rock types may yield vastly different products depending on the conditions of metamorphism. As with igneous crystallization, the number of mineral species created during metamorphism is limited by the constraints of chemical laws and thermodynamics. Given the pre-existing chemistry of the lithologic unit undergoing metamorphism, each new range of temperature and pressure will produce a limited number of mineral phases.

There are four major types of metamorphism recognized: cataclastic metamorphism, produced by the shattering and recrystallization of pre-existing units; contact metamorphism, produced by high temperature gradients at contacts with igneous bodies; regional metamorphism, produced on a large scale, involving elevated temperatures and pressures; and metasomatism, the production of new rocks by the introduction and translocation of elemental species (including pneumatolysis).

Cataclastic Metamorphism

Normally rocks located in proximity to a major fault zone in the crust of the earth are subjected to tectonic forces which bring about changes in the pre-existing mineral assemblage and rock fabric. Minerals may be reduced in size due to recrystallization or crushing; feldspars may be made to evolve phases (development of perthites); mineral crystal forms (e.g., "twins") may be bent, etc. These effects are usually local and may be traced directly to an active fault.

Contact Metamorphism

When igneous rocks intrude into pre-existing rock types, new mineral components are often formed in the host. This may be related to temperature; presence of volatiles and acids of various composition (water, fluorine, boron, carbon dioxide, etc.); and length of time the host is in contact with the intrusive. Other important factors which control the formation of new minerals include the texture and composition of the host rock, the highest temperature it was sub-

Table 1-16

MINERAL CONTENT RANGE OF THE THREE MOST COMMON SEDIMENTARY ROCKS

Mineral Species	Major Sedimentary Rock Type		
	Shale	Sandstone	Limestone
Quartz	22—32	67—70	± 4
K + Na Feldspar	18—30	8—12	± 2
Sericite and clay minerals	25—28	6—8	± 1
Calcite-dolomite	6—7	± 11*	93
Chlorite and related species	± 6 or less	± 1	0

*It should be noted that the presence of carbonate minerals in a rock type such as sandstone often reflects its occurrence as a "cementing agent," rather than as a discrete sand-size grain.

Table 1-17

AVERAGE MINERAL CONTENT OF CRUSTAL SEDIMENTARY ROCKS

Mineral Species	% Occurrence
Quartz (and other silica polymorphs)	35
Feldspar (K,Na,Ca)	16
Ferromagnesian minerals (amphiboles and pyroxenes)	15
Micas	
"Others" (clays, carbonates, etc.)	34

The bulk chemistry represented by the average mineral content of crustal sedimentary rocks is very close to the bulk chemistry of granodiorites, the most common crustal igneous rock.

jected to during its previous history, the shape of the interface with the intrusive body, the composition of the intrusive, and the crustal depth at which the contact occurred. Here, at the contact, profound metamorphic changes may take place. For example, the metamorphic minerals produced in carbonate rocks (limestones) reflect the increasing temperature gradient at the contact. Specific minerals appear with "granite intrusives" as distinct from those which originate by contact with "basaltic intrusives" (Table 1-18). The inclusion of "mineralizers" produces an additional mineral population characteristic of contact pneumatolysis.

Normally, one associates contact metamorphism with high temperatures and low pressures. Yet, significantly different mineral populations may be produced even during this "simple" metamorphic event. For example, the mineral

assemblage produced in shale rock depends to a great extent on its initial composition as well. Normally, one can predict, on the basis of the chemistry, which mineral phases will occur if a specific metamorphic temperature and pressure were to be achieved; i.e., specific cations (represented as oxides) recombine at specific temperatures and pressures to produce specific mineral phases. The basic difference in the production of different mineral populations under different physical-chemical conditions is the different combination ratios. For example, the combinations of periclase (MgO) and quartz (SiO₂) will, in different proportions, produce minerals such as olivine (Mg₂SiO₄) or enstatite (MgSiO₃). These minerals form under different conditions and appear in different rocks depending on the temperature of metamorphism. This has been called the "facies concept" be-

cause for a given chemical system, there are limited numbers of mineral phases which can be formed (based on the physical-chemical constraints). The minerals formed will be dependent on their stability ranges (a function of temperature and pressure).

Based on this concept, contact metamorphic facies for shale produce mineral assemblages which reflect the original chemistry of the shale rock itself (Table I-19).

Regional Metamorphism

It has been said that regional metamorphism is "contact metamorphism on a regional scale." Basically, the temperatures to which the pre-existing rocks are subjected are elevated, as are the pressures. There are normally "several zones" of metamorphic terrains recognized (see Table I-20). These have been termed the low grade metamorphic zone; the medium grade metamorphic zone; and the high grade metamorphic zone. Again, using argillaceous rocks as a model, it has been shown that certain mineral species tend to characterize metamorphic rocks when temperatures and pressures increase (Table I-20). These may range from low temperature zeolite minerals to high temperature pyroxene and garnet rocks. Metamorphism can proceed to such an extreme that the rock partially melts *in situ*, granitization takes place, and "igneous" granite cannot be readily distinguished from metamorphic granite. It should be noted that most granites may have originated from melts derived from pre-existing rocks.

Diverse minerals are formed in metamorphic rocks: those commonly found in igneous rocks and those that represent additional phases produced by recrystallization and through introduction of new cation species. Their mineral characteristics are shown in Table I-21.

METASOMATISM AND PNEUMATOLYSIS

Occasionally, contact of host rock units with igneous intrusives containing large quantities of volatile fluids (both liquid and gas) produces deposits of new minerals in rich diversification (see Table I-18). In this environment, many of the semi-precious and precious gemstones are formed. Often, new mineral assemblages superimpose on the older host assemblage. Large quantities of quartz may be formed during the new crystallization phase. Metasoma-

tism and pneumatolysis are both processes associated with contact metamorphism.

ROCKS AND MINERALS AS AGENTS OF DISEASE

It is obvious that the crust of the earth is a complex of interrelated rock types each of which has rich mineral diversity. As a result of this complexity, human exposure to rock and mineral dust is correspondingly complex. Yet, a common skein runs through the recognized disease patterns which suggests that only a limited number of these minerals and rocks are "dangerous." As a good illustration, quartz (found as a mineral constituent in almost every important rock type in the crust) has produced the most prevalent pneumoconiosis, silicosis. Silicosis is recognized in a range of occupational settings (Table I-36).

There are a number of pneumoconioses which are thought to be induced by minerals other than quartz. However, on close examination of the geological setting, the agent suspected may only play a minor role in the disease process. Exploitation of clay minerals, coal of all ranks, abrasives, ores of many varieties, and building stones, to name but a few, carries with it the danger of silica exposure (Table I-36). In these instances, quartz (as well as the other silica polymorphs, cristobalite and tridymite) occurs as either a trace contaminant or in forms which tend to escape detection (e.g., submicroscopic particle sizes). In these cases, the disease pattern tends to differ from "classical silicosis" and the general term "mixed-dust pneumoconioses" is often used.

These difficult problems are observed in the field of mining. Here, superimposed on the host rock complexity, is exposure to a multitude of "ore minerals."

ECONOMIC GEOLOGY

Large-scale exploitation of the crust for mineral resources began with the advent of the industrial revolution. With the world-wide spread of industrial societies and the provocation of our "chemical age," the quantity of raw materials recovered in the 20th century exceeds by many orders of magnitude the total exploitation since the vestigial beginnings of civilization. The exploitation and redistribution of the earth's natural resources includes precious metals, industrial metals, nonmetallic substances of all

Table I-18

**METAMORPHIC MINERALS PRODUCED IN CARBONATE ROCKS
AND DURING PNEUMATOLYSIS—CONTACT METAMORPHISM**

T °C		Mineral	Contact with mineralizers*
~250°	↑ Contact with granite	Talc	Tremolite
270°		Tremolite	Phlogopite
300°		Forsterite	Scapolite(s)
410°		Diopside	Axinite
450°		Brucite	Sphene
560°		Periclase	Apatite
600°		Wollastonite	Danburite
			Topaz

	↓ Contact with basalt	Monticellite	Tourmaline
		Akermanite	Fluorite
~700°		Tilleyite	Epidote
		Spurrite	
~800°		Rankinite	
		Larnite	
		Merwinite	

*Primarily not temperature dependent.

Table I-19

EXAMPLES OF CONTACT METAMORPHISM OF ARGILLACEOUS ROCKS

Temperature	Facies	Composition	Resulting Mineral Assemblage
↓ Increasing	Pyroxene-Hornfels	Lime-poor	Hypersthene, cordierite, quartz andalusite, corundum
		Lime-rich	All above, w/o corundum + anorthite, grossularite, wollastonite, diopside, vesuvianite
	Sanidine	Lime-poor	Periclase, olivine, pigeonite, cordierite, quartz, sillimanite, mullite, spinel, corundum
		Lime-rich	Sillimanite, mullite, cordierite, pigeonite, periclase, wollastonite, anorthite

Table 1-20

CORRELATION OF COMMON SCHEMES OF CLASSIFICATION OF METAMORPHIC ROCKS, AS RELATED TO REGIONAL METAMORPHISM OF ARGILLACEOUS ROCKS (SHALES)

T °C	Metamorphic Facies		Isograds-Mineral Indicators of Metamorphic Grades	Metamorphic Grade	Metamorphic Zone	Packing Indices	Pressure
	<i>Facies</i>	<i>Subfacies</i>					
150°—200 °C	Zeolite		Zeolites Chlorite	“Low”	Epizonal (phyllites)	Glaucophane Schist Chlorite Schist	 Increasing
200°—400 °C	Greenschist	sericite-chlorite biotite-chlorite	Biotite Epidote			Greenschist Albite Schist	
300°—500 °C	Epidote Amphibolite		Almandine garnet Staurolite	“Medium”	Mesozonal (Schists)	Mica Schist Amphibolite	
400°—600 °C	Amphibolite	cordierite-anthophyllite staurolite-kyanite sillimanite-almondine	Kyanite Sillimanite (S ₁) Sillimanite (S ₂)		Katazonal (gneisses)	Garnet Schist Sillimanite Schist	
600°	Granulite (gabbro granulite)		Pyroxene-garnet	“High”			
+ 800 °C	Ectinites	(v. high temperatures and pressure) (partial melting, migmatites + complete recrystallization- <i>in situ</i> granitization)	<i>In situ</i> melting, recrystallization, ductile deformation				

Table I-21

COMMON MINERALS IN METAMORPHIC ROCKS BY GROUPS AND SPECIES

Silica Minerals	Pyroxenes and pyroxenoids
Quartz	Enstatite
	Wollastonite
Aluminum Silicates	Diopside
Andalusite	Augite
Staurolite	Jadeite
Kyanite	
Sillimanite	Amphiboles
Cordierite	Actinolite (including its asbestiform variety)
	Anthophyllite (including its asbestiform variety)
Micas, chlorites and other sheet silicates	Tremolite (including its asbestiform variety)
Chloritoid	Glaucophane
Muscovite	Riebeckite (including its asbestiform variety, crocidolite)
Biotite	Cummingtonite
Phlogopite	Grunerite (including its asbestiform variety, amosite)
Paragonite	Hornblende (all its chemical varieties)
Talc	
Serpentine (including lizardite, antigorite, chrysotile)	
	Olivines
Feldspars	Forsterite
Plagioclase (almost all, especially anorthite, <i>bytownite</i> and labradorite in calcic metasediments; andesine, <i>oligoclase</i> , albite in metasediments)	Monticellite
Orthoclase (and other high-temperature potash feldspars)	
Microcline (and perthite, antiperthite feldspars)	Garnets and related compounds
	Pyrope
	Almandine
	Grossularite
	Zoisite
	Clino-zoisite
	Epidote

varieties, fossil fuels, etc.

There are many geological processes responsible for the formation of mineral deposits: magmatic processes; magmatic emissions, including hydrothermal processes, sublimation, and contact metasomatism; concentration of ores by processes of sedimentation (e.g., changes in physical-chemical environment and the precipitation of iron and manganese); accumulation of chemical substances through evaporation; concentration of ores through depositional concentration (including residual concentration); enrichment of ores at the earth's surface through weathering processes (oxidation and supergene enrichment); and general conditions of metamorphism (with and without the introduction of new elements). In summary, any earth process involving physical and chemical mechanisms which mobilize and concentrate previously dispersed element, may form ore deposits. This exploita-

tion has increased man's exposure to rocks and minerals with subsequent increase in disease. Agents of disease may include the host rock and its minerals.

The origins of mineral deposits of all varieties are often related to the inherent characteristics of crustal rocks. Structural planes (bedding, faults, joints, etc.) may control mineral localization; characteristics of the rocks themselves, including their composition and stratigraphic and textural characteristics, are also major factors which control ore deposition. In addition, the presence of certain species of anaerobic bacteria during lithification may play a major role in ore deposition (e.g., as with certain sulfide deposits which have been concentrated through bacterial reduction).

In the same geological time period, similar metals and materials are often concentrated in different geographic localities where similar con-

ditions existed. Therefore, some mineral deposits have been correlated to worldwide changes in some of these conditions, e.g., climate. The precipitation of iron-rich sediments in the southern hemisphere in Pre-Cambrian time gave rise to deposits of asbestos which occur in South Africa, Australia, and South America.

Many exploitable metallic and nonmetallic mineral deposits are commonly restricted to local concentrations in crustal rocks. They contain cationic metals, which may or may not be chemically bound with other elements. These ore minerals may be juxtaposed or admixed with other minerals, or host rocks, which are essentially waste products of no economic value. These are called gangue. Common ore minerals listed according to the main metal for which they are exploited, are listed in Table I-22. It is not sufficient for these minerals to occur in a host rock for them to be considered "ore." This is dependent upon their concentration, their economic value in the world market, their cost of recovery, shipping, and processing, etc. As important as the ore minerals are, so are their common associated gangue minerals. Although not of direct economic importance, the forms of the gangue mineral, their chemical nature, and their uses as by-product source materials, as well as the cost of their disposal may also determine the value of an ore body. Often, the economic potential of an ore body may be determined by the nature of the gangue minerals associated with the ores. A partial listing of common gangue minerals is found in Table I-23.

METALLIC MINERAL DEPOSITS

There are thousands of important metal-producing mineral deposits in the continental United States and in Alaska and Hawaii. Many of these deposits are currently worked or were until recently worked.

Industrial Metals

1. **Iron**—Geological origins include those originating as sedimentary deposits, igneous segregations, and metamorphic concentrates. Principal producing areas are listed in Table I-24.
2. **Copper**—Most major deposits are located in the Southwest, associated as disseminated ore in a specific igneous rock type. Much copper is also recovered as one of many metals associated with

lead-zinc ores in the Mississippi Valley. These deposits are listed in Table I-25.

3. **Lead-zinc**—Both lead and zinc are often by-product metals of copper and molybdenum and occur as primary metals in several major deposits in both the central and western United States. Important deposits are listed in Table I-26.

Precious Metals

In addition to the industrial metals, precious metal mining is also extensive in both the continental United States and in Alaska. Gold, silver, and platinum have all been recovered as both primary ores (mined specifically for these metals) and as associated "trace metals" in metaliferous deposits mined for other metal. With the increasing price of gold and silver, many of these secondary recovery operations have become the principal economic factor in a successful operation. Major precious metal deposits are listed in Table I-27.

Almost every metal required of an industrial society is mined in the continental United States (Table I-28). Although production of some of these metals does not meet national requirements in terms of total tonnage output, domestic deposits do exist which are competitive with world markets.

Ore deposits, and their ore minerals, rarely exist as single metal populations. Cationic species, on the basis of ionic radii, valence, and electronegativity, tend to coexist in the same geological environment. Therefore, there occurs in nature a number of common mineral associations (Table I-29).

NONMETALLIC MINERAL DEPOSITS

Of the important nonmetallic mineral deposits, the fossil fuels certainly head the list in terms of importance. Coal, of all ranks, oil, and gas provide most of the energy required by industrial societies.

Both coal and petroleum products originate in sedimentary rocks from pre-existing organic compounds, including plant and animal remains. Coal deposits are frequently admixed with gangue rock high in silica. Deposits of coal are extensive in the continental United States (Table I-30). The anthracite and bituminous coals of the Appalachian Field, the bituminous coals of the interior fields, and the vast sub-bituminous fields

Table I-22
COMMON ORE MINERALS

Metal	Common Ore Mineral	Composition
Aluminum	Bauxite	$Al_2O_3 \cdot 2H_2O$
Antimony	Stibnite	Sb_2S_3
Bismuth	Bismuthinite	Bi_2S_3
Chromium	Chromite	$FeCr_2O_4$
Cobalt	Smaltite	$CoAs_2$
	Cobaltite	$CoAsS$
Copper	Native copper	Cu
	Bornite	Cu_3FeS_4
	Brochantite	$CuSO_4 + Cu(OH)_2$
	Chalcocite	Cu_2S
	Covellite	CuS
	Cuprite	Cu_2O
	Enargite	$3Cu_2S + Ag_2S_3$
	Malachite	$CuCO_3 + Cu(OH)_2$
	Azurite	$2CuCO_3 + Cu(OH)_2$
Gold	Native gold	Au
	Calaverite	$AuTe_2$
	Sylvanite	$(Au, Ag)Fe_2$
Iron	Magnetite	Fe_3O_4
	Hematite	Fe_2O_3
	Siderite	$FeCO_3$
	"Limonite"	$FeO + Fe(OH)_2$
	Goethite	$HFeO_2$
Lead	Galena	PbS
	Cerussite	$PbCO_3$
	Anglesite	$PbSO_4$
Manganese	Pyrolusite	MnO_2
	Psilomelane	$Mn_2O_3 \cdot nH_2O$
	Braunite	$3Mn_2O_3 \cdot MnSiO_3$
	Manganite	$Mn_2O_3 \cdot H_2O$
Mercury	Cinnabar	HgS
Molybdenum	Molybdenite	MoS_2
	Wulfenite	$PbMoO_4$
Nickel	Pentlandite	$(Fe, Ni)S$
	Niccolite	$NiAs$
Silver	Native Silver	Ag
	Acanthite	Ag_2S
	Ceragyrite	$AgCl$
Tin	Cassiterite	SnO_2
	Stannite	$Cu_2S \cdot FeS \cdot SnS_2$
Tungsten	Wolframite	$(Fe, Mn)WO_4$
	Huebnerite	$MnWO_4$
	Scheelite	$CaWO_4$
Zinc	Sphalerite	ZnS
	Smithsonite	$ZnCO_3$
	Hemimorphite	$ZnSiO_3(OH)_2$
	Zincite	ZnO

Table I-23
COMMON GANGUE MINERALS

Silica forms	Quartz, amorphous silica
Carbonate minerals	Calcite, dolomite, siderite, rhodochrosite
Silicates	Feldspars, garnet, chlorite, clay minerals
Sulfates	Barite, gypsum
Iron oxide hydrate	Limonite minerals
"Others"	Host rock, fluorite, apatite
Sulfide phases	Pyrite, marcasite, pyrrhotite, arsenopyrite

of the Rocky Mountains and east Texas, are immense in terms of tonnage reserves. Although the likelihood of coal becoming the energy producing base for our nation is small, especially with the advent of nuclear energy (and energy in other forms), the organic compounds present in coal are of immense value to various portions of the chemical industry.

Oil and natural gas fields, both on and off the continental land mass, are also extensive (Table I-30). Although a great quantity of the petroleum requirements for the United States is currently imported, complete exploitation of the continental deposits here in North America has not yet been achieved. As an example, if shale oil could be economically extracted, it would provide the country with total petroleum needs for several centuries. Oil residues, composed of complex heavy hydrocarbons, tend to have chelated a number of heavy metals frequently observed in petroleum and its by-products. Each of these materials present different problems in terms of agents of disease.

Another important group of nonmetallic minerals, especially important to the chemical industry, are those which occur as evaporite deposits (Table I-31). Complex mineral assemblages consisting of important cations and anion complexes coexist as complex salt minerals in these deposits. Soda ash, potash minerals, and nitrite minerals, to name but a few, are derived from such deposits. Evaporites occur in the geological column (indicating a paleo-environment where evaporation exceeded water replenishment) as well as in current arid area deposits.

The variety of nonmetallic minerals and materials is enormous (Table I-32). Some of these substances are considered useless due to their

crustal distribution. However, if concentrated so that mining them is economically profitable, they become "nonmetallic ores." Even limestone, when occurring with a specific amount of free silica and poor in alkali cations, may be quarried and recovered as cement rock. As with the ore minerals, nonmetal associations are common as well (Table I-33). Materials of like mineral composition, rock type, and mode of origin, are exploited separately yet occur within the same deposit.

Nonmetallic minerals and materials take on added complexity. For example, single materials may have multiple uses: limestone may be used as a building stone, a cement rock, a chemical source, etc. (Table I-34). Occasionally, the same application may be fulfilled by multiple materials. For example, bulk insulating properties may be satisfactorily found in any number of mineral and rock species: asbestos, diatomaceous earth, pumice, etc. This is also true of industrial material called "refractories" (Table I-34).

As a final illustrative example, even the rocks which constitute the crust of the earth may have economic value based on important, inherent characteristics. These often include both esthetic features and durability. For building purposes, granites, limestones of all varieties, marbles, etc., have been used in the United States (Table I-35). It is probably this final example which clearly demonstrates the close association man has had with the crust of the earth. He first used natural caves as his home, recovered materials of all types for a range of purposes, and exists today in an industrialized society actualized by energy-derived fossil fuels. However, he is paying a price for these manifold energy and technological benefits.

Table I-24
MAJOR IRON* DEPOSITS—BY STATES

State	Principal District—Mine
Alabama	Clinton iron-ore of Paleozoic age Principal Appalachian deposits of Hematite
Michigan, Minnesota, Wisconsin	Superior Upland of Pre-Cambrian age including: Cuyuna, Vermilion, Mesabi, Marquette, Menominee and Gogebic ranges. Hematite and magnetite— many pits.
Missouri	Iron Mountain deposit
Nevada	Ely
New Jersey	Dover
New Mexico	Fierro, Hanover
New York	Lyon Mountain
Pennsylvania	Cornwall
Texas	Northwest district (NW. Texas)
Utah	Iron Springs
Virginia	Oriskany deposits
Wyoming	Iron Mountain

*Iron occurs with manganese and titanium.

Table I-25
MAJOR COPPER* DEPOSITS—BY STATES

State	Principal District—Mine
Alaska	Kennecott District
Arizona	Ajo, Bisbee, Clay, Globe, Jerome, Magma-Superior, Miami-Inspiration, Morenci, Ray, United Verde
California	Plumas, Walker Mine
Colorado	San Juan
Minnesota-Michigan	Superior Upland District
Montana	Butte
Nevada	Ely, Rio Tinto
New Mexico	Chino, Santa Rita
Tennessee	Ducktown District
Utah	Tintic, Bingham
Washington	Holden

*Copper occurs with lead, zinc, molybdenum, tungsten, gold, and silver.

Table I-26
MAJOR LEAD-ZINC* DEPOSITS—BY STATES

State	Principal District—Mine
Arizona	Bisbee
California	Darwin, Inyo
Colorado	San Juan, Leadville, Red Cliff
Idaho	Coeur d'Alene district (include: Bunker Hill, Sullivan, Morning, Hecla mines)
Missouri, Oklahoma, Kansas	Southeast Missouri district. Tristate district (SW. Missouri; NE. Oklahoma; SE. Kansas)
Nevada	Pioche, Goodsprings
New Jersey	Franklyn Furnace
New Mexico	Hanover, Magdalena
New York	Balmat-Edwards
Pennsylvania	Friedensville
Tennessee	Ducktown district (Include: Jefferson City, Mascot, Embree)
Utah	Bingham, Park City, Tintic
Virginia	Austinville
Wisconsin, Illinois	Southern Wisconsin (northern extension of Mississippi Valley deposit; Tristate extension)

*Lead-zinc occurs with copper and silver.

Table I-27
MAJOR PRECIOUS METAL DEPOSITS—BY STATES

State	Gold†	Silver*	Platinum
Alaska	Juneau, Treadwell, Yukon, White Channel, Klondike, Nome Creek, Seward, Fairbanks		Goodnews Bay
Arizona	Oatman		
California	Mother Lode area (Sierras), Grass Valley	Darwin	Mother Lode area (Sierras)
Colorado	Bull Domingo, Bassick, Cresson, Quartz Hill, Ouray, Camp Bird, Cripple Creek, San Juan	Quartz Hill, Georgetown, Leadville, San Juan San Juan	
Idaho		Couer d'Alene, Sunshine,	Stillwater
Montana	Golden Curry, Cable	Butte	
Nevada	Sierra Nevada range, Goldfield, Aurora, Tuscarora	Rochester, Virginia City, Tonopah (Comstock)	
Oregon			Plateau Basalt Area
South Dakota	Homestake, Black Hills		
Texas		Shafter	
Utah	Cactus, Gold Hill	Bingham, Silver Reef, Park City, Tintic, Emma	

†Includes: silver and copper.

*Includes: lead, zinc, copper, gold.

Table I-28

TWENTY ADDITIONAL METALS (OTHER THAN THOSE LISTED PREVIOUSLY)*

Metal	Principal Areas of Exploitation—By State**
Aluminum	Arkansas, Alabama, Georgia, Tennessee, Virginia, Mississippi, New Mexico
Antimony	Idaho, California, Nevada, Alaska
Arsenic	Primarily a by-product of copper processing (see Table I-25)
Beryllium	South Dakota
Bismuth	Arizona, Colorado, Nevada, Utah
Cadmium	Primarily a by-product of zinc processing (see Table I-26)
Chromium	California, Oregon, Maryland, North Carolina, Alaska
Cobalt	Missouri
Manganese	Arkansas, Colorado, Georgia, Montana, South Dakota
Mercury	California
Molybdenum	Arizona, Colorado, New Mexico, Utah
Nickel	Oregon, Montana, Alaska
Radium-Uranium	Colorado Plateau (New Mexico, Colorado, Arizona, Utah, Nevada, Montana, North Dakota, South Dakota, Wyoming)
Selenium-Tellurium	Primarily a by-product of copper processing (see Table I-25)
Tantalum-Colombium	South Dakota
Tin	Alaska
Titanium	New York, Florida, Virginia
Tungsten	California, Colorado, Idaho
Vanadium	Arizona, Colorado, Idaho, Utah, Wyoming
Zirconium	North Carolina, Florida

*Excluding rare earths and specialty metals.

**Primary sources listed. If major production comes as a "by-product," it is so indicated. Those metals with primary sources may also be produced as a "by-product," e.g., Mn, from iron-ore processing in the Superior Upland.

Table I-29

COMMON METAL ASSOCIATIONS

Common multiple metal mixtures:

Silver-Gold-Copper-Lead
 Silver-Gold-Copper-Lead-Zinc
 Silver-Tin-Lead-Zinc
 Gold-Platinum-Copper-Nickel

Common binary metal associations:

Silver-Gold
 Lead-Zinc
 Copper-Gold
 Iron-Manganese
 Iron-Titanium
 Nickel-Copper
 Nickel-Cobalt
 Chromium-Platinum
 Tin-Tungsten
 Molybdenum-Copper
 Zinc-Cadmium

Common by-product metals, metalloids:

Arsenic
 Antimony
 Bismuth
 Calcium
 Selenium

**HUMAN DISEASES ASSOCIATED
 WITH ROCKS AND MINERALS**

Many effects have been described in humans exposed to rock and mineral dust generated during the recovery of crustal materials. Some of these are well known and receive much attention—e.g., silicosis, resulting from exposure to the silica polymorphs and the asbestos diseases, resulting from exposure to the asbestos minerals. Yet, most exposures in the crustal environment are not pure exposures: they involve exposure to a number of inorganic dust components. Such disease stigmata are either so complex as to be called “mixed dust pneumoconioses” with characteristics of several “pure exposures” or have been given the name of the principle dust alone. Some of these, and the associated complexities, are listed in Table I-36. Exploration of the biological effects of these materials is in its infancy.

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Table I-30

MAJOR FOSSIL FUEL DEPOSITS
COAL—BY FIELDS—ALL RANKS

Appalachian Field:*	Pennsylvania, Ohio, West Virginia, Virginia, Maryland, Kentucky, Tennessee, Georgia, Alabama
Interior Fields:	
Eastern	Illinois, Indiana, Western Kentucky
Western	Iowa to Arkansas (Great Plains States)
Southwest	Texas
Northern	Michigan
Rocky Mountain Field:	Montana to New Mexico
Pacific Coast Field:	Washington (+ Alaska)

Oil and Gas Fields (On and Off Shore)

Appalachian Field	<i>Includes:</i>
Mid-Continent Field	Alaska
Gulf Coast Field (incl. East Texas)	Arkansas
Rocky Mountain Field	California
California and Pacific Coast	Colorado
Alaskan Field (north slope)	Illinois
	Kansas
	Louisiana
	Michigan
	Mississippi
	New Mexico
	Oklahoma
	Pennsylvania
	Texas
	Wyoming

*Tend to be anthracite and bituminous. Other fields (excluding local small deposits) tend to be bituminous and lower ranks.

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Table I-31
MAJOR EVAPORITE DEPOSITS

Product	Location
Alkali minerals (principally soda)	Owens Lake, Mono Lake, California; Soda Lakes of Nevada
Borate minerals	Owens Lake, Searles Lake, Borax Lake, California; Dry Lakes of Oregon and Nevada
Gypsum, anhydrite	New York; Great Salt Lake (Utah); Gulf Coast (Mississippi Valley)
Halite	New York; Ohio; Michigan; New Mexico; Gulf Coast; Great Salt Lake (Utah); Imperial Valley, California
Nitrate minerals	Searles Lake (and others) California; Dry Lakes of Utah and Nevada
Potash minerals	Searles Lake, Mono Lake, Death Valley, California; Moab, Utah; Columbia Marsh, Nevada
Sulfate minerals (excluding gypsum and anhydrite)	Soda Lake, Searles Lake, California; Downey Lake, Wyoming; Verde Lake, Arizona

Table I-32

SOME EXPLOITED NONMETALLIC MINERALS AND MATERIALS

Abrasives	Garnet, corundum, sand, tripoli, flint, emery	New York, Massachusetts, Virginia, North Carolina, New Hampshire, Idaho
Asbestos	Asbestiform silicate fibers, predominantly chrysotile	Vermont, Arizona, California
Barite, Witherite	BaSO ₄ , BaCO ₃	Missouri, Georgia, California, Arkansas, Virginia
Building stone	All varieties, e.g., granite, limestone, sandstone	(See Table I-35)
Cement rock	Siliceous limestone	New York, Pennsylvania
Clay minerals	Kaolin, attapulgite, bentonite, ball and fire clays, estaurine clays, Fuller's earth	Indiana, Illinois, Maryland, New Jersey, North and South Carolina, Virginia, Wyoming, California, Connecticut, Delaware, Georgia, Kentucky, Tennessee, Pennsylvania, Ohio, Missouri, South Dakota
Coal	Anthracite to peat	(See Table I-30)
Diatomaceous earth	Amorphous opaline silica	California
Fertilizer	Potash from evaporite minerals and others	(See Table I-31)
Feldspars	Orthoclase, microcline	(See Table I-35)
Fluorspar	CaF ₂	Illinois, Kentucky, Colorado, New Mexico
Gemstones	Mostly semi-precious, e.g., tourmaline	California, Maine
Glass	SiO ₂ (quartz)	West Virginia, Pennsylvania, Illinois, Missouri
Graphite	Carbon	New York, California, New Mexico, Rhode Island, Alabama, Texas
Gypsum	CaSO ₄ · 2H ₂ O	(See Table I-31)
Halite	NaCl	New York, Michigan, California, Utah
Micas	Muscovite, biotite, vermiculite	Montana, Arizona, North Carolina
Phosphates	Phosphate minerals	Florida, North Carolina
Refractories	Aluminum silicates	California, Virginia, North Carolina, Georgia, South Dakota, Nevada
Sulfur	Sulfur	Louisiana
Talc, Soapstone Pyrophyllite	Magnesium silicate hydrate, Aluminum silicate hydrate	Vermont, Georgia, California, New York, Montana, North Carolina
Zeolites	Erionite, mordenite, others	Wyoming, Nevada, Utah

Table I-33

COMMON NONMETAL ASSOCIATIONS

Oil and natural gas	Fossil fuel reservoirs
Salt, potash, gypsum	Evaporite deposits
Feldspar and mica	Granite pegmatites
Soapstone and talc	Steatized Mg-rich rocks
Coal, fire clays, ball clays	Coal seams

Table I-34

EXAMPLES OF COMPLEXITY OF NONMETALLIC MINERALS AND MATERIALS

Single material with multiple uses

e.g., "*Limestone*" Building stone, trim stone, cement rock, chemical source (e.g., magnesium), fertilizer source (lime), lithographer's media

Multiple materials for single uses

e.g., "*Bulk insulating material*" Asbestos (primarily chrysotile)
Diatomaceous earth
Gypsum (calcined)
Magnesium carbonate
Perlite (calcined)
Pumice
Vermiculite

e.g., "*Refractories*" Clays (pure, especially aluminum silicates (e.g., kaolin, dickite)
Silica forms (e.g., quartz, diatomite)
High alumina refractories (e.g., sillimanite, andalusite, kyanite, dumortierite)
Zirconia (from zircon and baddeleyite)
Graphite
Rutile
Beryllium compounds
Titanium compounds
Pyrophyllite and talc block
Olivine in magnesia matrices

Table I-35
BUILDING STONES

Stone	Important Producing States
Dolerite (trap rock) and others	New Jersey, Connecticut, Massachusetts, Pennsylvania
Granite (including gneisses)	Vermont, Maine, Minnesota, Massachusetts, New Hampshire, Rhode Island, Wisconsin
Limestone	Florida, Indiana, Minnesota, Missouri, Texas
Travertine	Colorado, Montana
Marble	Georgia, Vermont
Sandstone	Connecticut, Kentucky, New York, Pennsylvania
Soapstone	Virginia

Table I-36
NATURAL MATERIALS ASSOCIATED WITH HUMAN DISEASE
ROCKS

Rock Type	Mineral Components	Comments
Coal	Anthracite Bituminous ± quartz	Coal workers' pneumoconiosis; "miner's consumption"; focal emphysema; anthracosis, silico-anthracosis; may be related to rank (anthracite > bituminous); "melanosis" or "black lung"; greater incidence of tuberculosis; may progress to "massive fibrosis."
Fullers earth	Butonites and related montmorillonites ± quartz + free silica	Pneumoconiosis without massive fibrosis and nodules (diffuse); mottled x-ray appearance; some related silicosis
Diatomaceous earth	Opaline diatom fragments	Some lung scarring developed; much greater in processing when calcined (conversion of opal to cristobalite); silicosis with progressive massive fibrosis.
Granite Quartzite Sandstone Slate	All with large amounts of quartz.	Silicosis; silico-tuberculosis; nodular silicosis; fibrosis; enlarged and hardened lymph glands. Silicotic nodules in spleen
Pumice	Volcanic glass, some devitrification to quartz	Resembles silicosis; some linear scarring.

Table I-36

NATURAL MATERIALS ASSOCIATED WITH HUMAN DISEASE (Continued)

ROCKS

Mineral Name	Major Uses	Comments
Limestone	Calcite ± quartz	Some bronchitis; some emphysema, some scarring reported; when calcined for industrial purposes, toxicity increases; caustic burns; dermatitis; ulceration of skin; injury to conjunctiva and cornea.
Marble	Calcite ± quartz	
Dolomite	Dolomite ± quartz	
Gypsum	Gypsum ± evaporites	Some bronchitis; when calcined for industrial purposes, toxic effect to skin increases some irritation to eyes, nose, and pharynx
Anhydrite	Anhydrite ± sulfur	
Bauxite	Hydrated aluminum oxides	Some reports of lung scarring

SILICATE MINERALS

Amosite	Used as asbestos	A major asbestos mineral; asbestosis lung cancer; cancer of the gastrointestinal tract; pleural and peritoneal mesothelioma; possible increase in other malignancies.
Anthophyllite	Used as asbestos	See amosite
Biotite	Insulation and filler	Pulmonary fibrosis; silicosis; strong association with free quartz, likely a major factor in producing fibrosis.
Chalcedony	Pottery and grinding material (abrasive)	Silicosis; "potters' asthma"; "potters' consumption"; silicotic nodules in spleen; silico/tuberculosis; progressive pulmonary fibrosis.
Chert	See chalcedony	See chalcedony
Chrysotile	See anthophyllite	See anthophyllite; this mineral is the asbestos type which accounts for over 90% of asbestos consumption in the United States.
Cristobalite	By-product produced	See chalcedony; cristobalite is more fibrogenic than quartz
Crocidolite	See amosite	See amosite

Table I-36
NATURAL MATERIALS ASSOCIATED WITH HUMAN DISEASE (Continued)
SILICATE MINERALS

Mineral Name	Major Uses	Comments
Diatomaceous earth (Opal)	See chalcedony	See chalcedony; the opaline composition is altered when the earth is processed; it is often converted to cristobalite, in whole or in part.
Feldspar (K,Na spar)	Ceramics	Silicosis; often attributed to the included quartz content of the pegmatite-derived mineral.
Flint	See chalcedony	See chalcedony
Fluorite	Industrial flux	Fluorosis; silicosis; the latter is often attributed to the associated quartz
Graphite	Crucibles; high temperature facings; electrodes; paints	Graphite pneumoconiosis; tuberculosis; resembles silicosis
Kaolin	Ceramics; filler	Some lung scarring observed, but only in areas associated with free quartz.
Kyanite	Ceramics	Some lung scarring observed.
Muscovite	See biotite	See biotite
Nepheline	Industrial uses	Nephelosis; some lung scarring.
Olivine	Industrial uses	Silicatosiis; some lung scarring.
Phlogopite	See biotite	See biotite
Pumice (obsidian and scoria)	Abrasive; insulation	Silicosis
Quartz	Abrasive; industrial uses	See chalcedony; this material is likely responsible for a number of diseases attributed to other minerals.
Sericite	Impurity associated with other minerals	Some fibrosis observed in men exposed to sericite dusts; however, attributed by some to the admixed free quartz.
Sillimanite (mullite)	See kyanite	See kyanite
Talc	Industrial uses; filler	Talcosis; talc pneumoconiosis
Tridymite	See cristobalite	See chalcedony; also, more fibrogenic than quartz.

Table I-36
NATURAL MATERIALS ASSOCIATED WITH HUMAN DISEASE (Continued)
ORE MINERALS

Metal	Mineral	Comments
Aluminum	Bauxite ore Corundum	Aluminosis; some lung scarring; corundum grinders may suffer a severe pneumoconiosis; emphysema; free silica (quartz) associated with corundum deposits, some scarring attributed to this.
Arsenic	Cobaltite Enargite Realgar Orpiment Arsenopyrite Smaltite	Local skin and mucous irritant; carcinogen; anemia (hemolytic agent); hemoglobinuria; most severe reactions are observed during the smelting of arsenic-containing ores; miners of the ore are reported to have "excess" lung cancers although published accounts are few; also, many of the ores are admixed with other materials which confound the data and represent "mixed dust pneumoconioses."
Beryllium	Beryl Chrysoberyl Bertrandite	Berylliosis; chronic lung disease; pulmonary lesions; acute poisoning; granuloma; pneumonitis; most severe reactions are observed in ore processing; ore minerals are associated with quartz-rich rocks which add a "mixed dust pneumoconioses" effect.
Cadmium	Greenockite	Most effects are related to mineral processing and recovery; generally a by-product of Pb and Zn smelting; no pneumoconiosis reported for the mineral dust itself; renal and pleural involvement.
Chromium	Chromite	Some reports of lung cancer among chromite miners, but most of the effects are among the "chromite workers" who process the ore; the ore also includes a number of other active mineral substances such as serpentine phases (chrysotile).
Cobalt	Smaltite Linnaeite Cobaltite Erythrite	Some reports of excess deaths due to lung cancer and cancer of the main bronchus; "hardmetal disease"; excess cancer among the cobalt ore processors.
Iron	Hematite Magnetite	Siderosis; scarring of the lung increases as the quartz content of the ore increased; some reports of increased lung cancer among taconite ore miners of Newfoundland; some experimental work supports this observation.

Table I-36
NATURAL MATERIALS ASSOCIATED WITH HUMAN DISEASE (Continued)

ORE MINERALS

Metal	Mineral	Comments
Lead	Galena Cerussite Anglesite	Some reports of pneumoconiosis among the miners of galena, likely produced by associated mineral dusts; most of the severe reactions are observed among the processors and users of the by-products; diseases of the central nervous system; nephritis; "plumbism"; anemia; Pb content of ambient air in smelting towns is generally high.
Manganese	Pyrolusite Braunite Manganite Hausmanite Rhodochrosite	Some reports of pneumoconiosis among miners of manganese ores, but most effects are observed among ore processors; affects the central nervous system (Parkinsonism syndrome); unusually high rate of pneumonia among ore processors.
Mercury	Cinnabar	A range of systemic diseases are recognized among miners and processors; nephrosis (renal lesions); "salivation"; "vertigo"; "paralysis"; "Hatters shakes"; erethism; stomatitis; "mercury poisoning"; perforation of nasal septum.
Nickel	Pentlandite Nicolite Millerite Garnierite	Some pneumoconiosis observed among miners but generally attributed to the admixed gangue minerals; some observations indicate a higher than normal lung cancer rate among miners of Ni in "hard rock areas"; higher incidence of lung and nasopharynx cancer amongst Ni smelters.
Phosphorus	Apatite	Some x-ray changes of lungs with minor scarring; some neurological disorders induced in men who process mineral for P recovery; phosphine and pesticide forms toxic-to-lethal.
Platinum	Platinum Sperrylite	No disease associated with water-worked placer deposits; direct mining in mafic rocks generally associated with serpentine minerals, some lung scarring observed which resembles asbestosis.
Selenium	Tiemannite Guanajuatite Clausthalite Naumannite Eucairite Chalcomenite	Pneumoconioses observed are to admixed gangue minerals; some observed in hard-rock mining of Pb, Cu, Hg, Ag, ores; most adverse effects observed in ore processors; severe irritation of nose and eyes; gastro-intestinal disorders; dental caries.

Table I-36
NATURAL MATERIALS ASSOCIATED WITH HUMAN DISEASE (Continued)
ORE MINERALS

Metal	Mineral	Comments
Silver	Silver Acanthbite	Some x-ray changes of lungs but attributed to the admixed gangue minerals; some disease observed in men processing ore; argyria—discoloration of the skin to a pale gray or blue-gray.
Tellurium	Montanite Emmonsite Durdenite Tetradymite	As in the case of selenium, the pneumoconioses observed are attributed to the admixed gangue minerals; some scarring in areas of hard rock of mining of Bi, Pb, Ag, Hg. Most adverse effects are observed in ore processors; gastrointestinal disorders; renal disorders (impairment or death).
Tin	Cassiterite	Severe x-ray changes in miners; tin pneumoconiosis; some associated silicosis when quartz admixed in as gangue.
Titanium	Rutile Sphene Ilmenite	Severe lung scarring, titaniosis; scarring regardless of the nature of the gangue minerals.
Tungsten	Wolframite Tungstite	Lung scarring observed among miners of tungsten pneumoconiosis; ore often associated with cobalt minerals—the suspect causative agent.
Uranium	Uraninite Carnotite Pitchblende Thorium ores Vanadium ores	Some silicosis reported for sandstone deposits of uranium; excess lung cancers reported for the Colorado Plateau.
Vanadium	Vanadinite Carnotite	Some permanent lung scarring; immediate reaction is a respiratory irritant; irritant to eyes; susceptibility to pneumonia.
Zinc	Sphalerite	Shortness of breath; some minor lung changes; some deaths reported from pneumoconiosis.

AIR SAMPLING AND ANALYSIS FOR GASES AND VAPORS

Michael J. Peach, III

Wallace G. Carr

Exposure to airborne contaminants in the work environment has been linked to a wide spectrum of occupational diseases. A serious problem has existed over the years in occupational health in that much of the medical and epidemiological research data collected on workers has not had companion occupational environmental data collected in the time interval over which exposures occurred. The evaluation of worker exposure to potentially hazardous agents in the workplace is essential to establishing cause/effect relationships between an occupationally related illness and a specific agent(s). Existing gaps in worker exposure data have greatly limited the establishment and promulgation of proper occupational health standards for our nation's work force.

The purpose of this chapter is to describe current procedures and methods employed by industrial hygienists to assess, measure, and characterize worker exposure to potentially hazardous contaminants in the occupational environment. The chapter is divided into two sections: sampling techniques for gases and vapors and techniques for particulate sampling.

INTRODUCTION

Air sampling for gases and vapors in the occupational environment is less difficult than for aerosols because at ordinary temperatures and pressure they follow the ideal gas law, they mix freely with ambient air, and in a short time can reach a state of equilibrium. Although the terms "gases" and "vapors" are frequently used synonymously, there are differences that should be acknowledged. For industrial hygiene purposes, a substance is a gas if, at standard conditions (70°F and 760 mm Hg), its normal physical state is gaseous. A vapor is a gaseous form of a substance which under standard conditions may exist as a solid or a liquid in equilibrium with its vapor. Because gases and vapors exist in a similar physical state, the term gas or gaseous substance will be used to include both gases and vapors and they can be collected with the same air sampling devices. The only exception to this is the rare circumstance where vapors at supersaturated concentrations may co-exist as liquids or mists.

Two kinds of air sampling instrumentation are employed to measure worker exposure to gaseous substances: (1) methods requiring laboratory analysis of collected samples, and (2) direct reading instrumentation capable of sam-

pling a volume of air, performing immediate analysis internally, and displaying results visually.

METHODS REQUIRING LABORATORY ANALYSIS OF COLLECTED SAMPLES

Basically, two air sampling methods are employed in industrial hygiene to collect gaseous samples from ambient work atmospheres for subsequent analysis. The first is the grab (instantaneous or short-term) sample in which a volume of air containing a gaseous contaminant is collected over a short period of time, usually from seconds to less than two minutes. Results of the sample's analysis are representative of the airborne concentration of the contaminant, at the sampling location at that point in time. The second is the integrated (average or long-term) sample in which a known volume of air is metered through an appropriate absorbing or adsorbing medium to remove the gaseous contaminant from the sampled airstream. Depending on the circumstances, the sample period may vary from a partial period sample of less than one hour to a full eight-hour sample. Analysis of these samples yield integrated, average, or long-term exposure levels reflecting the workers' overall exposure for that sample period.

Several important criteria that must be considered in the selection of a sampling method are: the solubility, volatility, and reactivity of the contaminant; the sensitivity of the analytical method (77); and the kind of information sought (e.g., peak concentrations or integrated exposure levels).

Grab—Instantaneous or Short-Term Samples

Grab sampling is best employed in monitoring several phases of a cyclic process and for determining peak concentrations where working levels of a contaminant generated by an industrial process vary over time. A wide spectrum of gas collection devices have been used to collect grab samples, including evacuated flasks or metal cylinders, syringes, plastic bags, and gas and liquid-displacement containers.

Evacuated Containers

Evacuated containers are usually heavy walled, glass containers ranging in size from 200 to 1000 cc in which the air has been partially or completely removed. These air collection devices have been successfully used for many years in the mining industry by the Bureau of Mines (BOM) (5)(77)(100) and more recently by the Mine Safety and Health Administration (MSHA) compliance officers to test underground work atmospheres for toxic and explosive gases (101). Containers currently used are 50 cc or 250 cc glass bulbs that have been evacuated with a vacuum pump and the neck sealed by heating and drawing the open end to a tip during the final stages of evacuation. To collect an air sample, the etched tip of the bulb is broken; the surrounding atmosphere enters and fills it to atmospheric pressure. The container is then resealed and submitted to the laboratory for analysis. A lightweight, steel evacuated container (Figure 1-1) lined with a nonabsorbing interior surface has reportedly been used with success for a number of years (61). Designed and used initially as a breath alcohol tester in forensic applications (84), its use has been extended to air sampling for a variety of organic vapors including benzene, methyl ethyl ketone, styrene, and vinyl chloride. Sample collection is achieved by pressing a button which activates the sampler. After the sample has been collected, the sampler

is submitted to the laboratory for analysis.

With the availability of more sensitive analytical instrumentation, smaller sample volumes have been found to be adequate. This led to the use of 10 cc *vacutainer syringe systems* (31)(32)(33)(101) by the BOM and MSHA for routine sampling of mine gases except for those which are highly reactive. Similar to conventional hypodermic syringes, the vacutainer system is an evacuated glass test tube-shaped vessel, capped with a self-sealing butyl rubber septum (Figure 1-2). To draw a sample, the tube is inserted into a holder equipped with a needle which punctures the rubber septum allowing air from the surrounding atmosphere to be drawn into the tube. After the sample is drawn, the glass tube is removed from the holder and the septum self-seals. Advantages of the vacutainer system are that the syringes are small, light-weight, economical, convenient, and simple to use. The use of conventional *hypodermic syringes for sampling* gases and vapors has been previously reported (34)(47).

Gas Sampling Bags

Gas sampling bags have been used successfully for a number of years to collect air samples containing organic and inorganic gases (19)(20)(21)(53)(75)(87)(95)(98)(102) and as a static system for the preparation of known concentrations of gases for the calibration of air sampling instrumentation (7)(10)(95). Grab bag sampling provides a simple, uncomplicated, and relatively economical means of collecting and transferring air samples to a laboratory for analysis.

An important feature of plastic bag sampling is that it offers the option of short-term sampling or sampling for a full work shift, depending on the size of the bag and the pump flow rate. Common field application of this technique is the use of a single portable analytical instrument to analyze multiple samples on site (where they are collected by an industrial hygiene team). Immediate on-site testing of a gas has an important advantage in that it greatly reduces the possibility of gas decomposition before analysis.

Plastic bags are commercially available and come in a variety of sizes and shapes with the 1-15 liter volume appearing to be the most useful for grab or short-term sampling and up to 170 liters for full-shift sampling. In addition, most

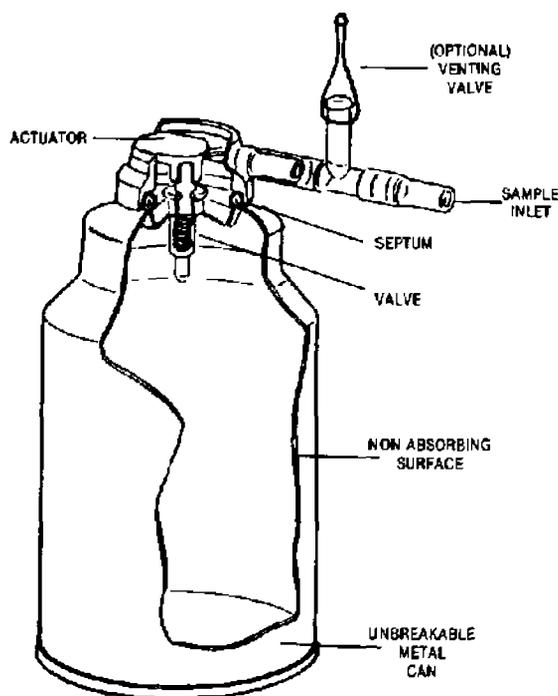


Figure I-1. Steel Evacuated Air Sampler (Vaccu-Sampler)

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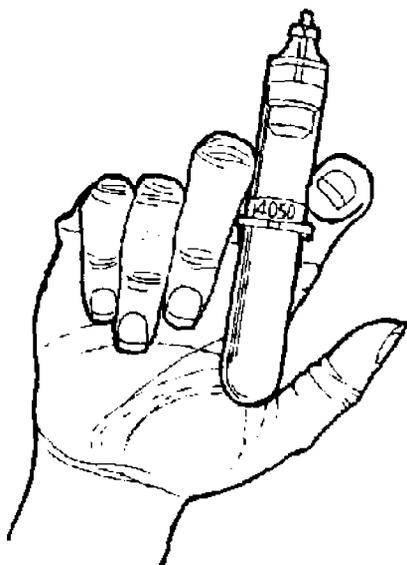


Figure I-2. Vacutainer syringe system used in the collection of mine atmosphere gases.

Source: *Mine Gases*, Safety Manual No. 2, U.S. Department of Interior, Mine Enforcement and Safety Administration.

plastic air sampling bags can be obtained with a number of convenient accessories, such as twist-lock open and shut-off valves, through which air can be easily sampled or discharged, and special permanent or replaceable rubber septums, through which air samples can be removed with a syringe.

Gas sampling bags are constructed from a number of materials including polyester, polyvinylidene chloride, teflon, and fluorocarbons (77). The selection of a bag constructed of a given material cannot be extended for use in collecting a broad range of gases because of the possible reactive nature of the gas with the bag. It is, therefore, necessary to know the type of material from which the bag is fabricated as well as its reactive, adsorptive, absorptive, and diffusive properties to the gaseous contaminant. Information on the storage properties of gases and vapors in plastic containers has been published (4)(6)(12)(23)(39)(54)(74)(83)(92).

Gas or Liquid Displacement Collectors

Gas or liquid displacement collectors (6)(77)(101) are primarily 250-300 ml *glass aspirator bulbs* fitted with end tubes which can be conveniently opened and closed with greased stop-cocks. Air samples are collected by aspirating the test atmosphere through the sample container with a suitable source of suction (bulb aspirator, hand pump, battery, or electrically operated vacuum pump) until its original content of air is replaced. Larger *aspirator vessels* can be used where large volumes of the test atmosphere or longer term sampling is required. Air samples can also be collected by liquid displacement. This method entails filling the container with a suitable liquid (usually water) and allowing it to drain out at the sampling location, whereupon the test atmosphere enters the container as the liquid is displaced. Application of this method is limited to gases which are insoluble or nonreactive with the displaced liquid. Although these methods were once routinely used for collecting air samples in work atmospheres and in laboratory studies, they receive little use today because of more convenient and accurate methods.

Because the quantity of material collected with gas sampling devices is often small, sensitive analytical methods are required to detect and measure concentrations of the gaseous contaminant collected. This has been a limiting factor

in using the grab sample in the past. Consequently, grab sampling has, to a large extent, been restricted to the collection of gross quantities of gases in air such as methane, oxygen, carbon monoxide, carbon dioxide, and nitrogen. However, the use of grab samples for the collection of low levels of gaseous contaminants has been greatly extended by advances in the refinement of sensitive analytical procedures and instruments based on chromatography and spectrophotometry.

Grab samplers should not be used to collect reactive gases (hydrogen sulfide, oxides of nitrogen, sulfur oxides, etc.) unless the samples can be analyzed within a short time after collection. Without prompt analysis, these gases can react with dust particles, moisture in the stopper, sealant compounds, and the glass container to alter a sample's chemical composition and result in an erroneous estimate of the concentration. This problem can sometimes be overcome by collecting the reactive gas in a conventional vacuum-type (evacuated) sample container prepared with an appropriate absorbing reagent to stabilize and preserve the sample until analysis can be accomplished (5)(14)(100).

An important feature of grab sampling is that the collection efficiency is normally 100%. However, sample decay can occur for several reasons. To limit or avoid this source of error, after introducing the sample of contaminated air into the container, it should be properly sealed to prevent sample loss and analyzed immediately in the field or submitted to the laboratory as soon as possible.

Unlike conventional liquid and solid sorbent sampling, gas flow measurements are not necessary with grab sampling devices because the air sample collected can be metered directly from the sample container into the analytical instrument, or measured volumes of the air sample can be drawn from the sampling device with a syringe and injected directly into the injection port of the analytical instrument. However, it is necessary to include the temperature and pressure (normally 25°C and 760 mm mercury) at which the air sample was collected in order that results of the sample analysis can be reported in terms of standard conditions.

Integrated—Average or Long-Term Sampling

Integrated sampling for airborne gaseous

agents is employed when (a) concentrations of the contaminant(s) to which the worker is exposed vary significantly over a work shift, (b) when ambient concentrations of the contaminant(s) are low and sampling over an extended period of time is required to satisfy the sensitivity requirements of the analytical method, and/or (c) to obtain a reliable estimate of the worker's exposure over a full work shift, in order to establish compliance or noncompliance with an 8-hour, time-weighted-average occupational health standard.

The collection of integrated samples usually involves the extraction and concentration of gaseous contaminants from a sample's airstream, employing the principles of *absorption*, *adsorption*, or *condensation*.

Absorption

In this method the gaseous contaminant is extracted from the sampled air stream and concentrated in solution by drawing it through an absorbing liquid or reacting it with an absorbing reagent. Four basic absorbers have been used: *simple gas wash bottles*, *spiral or helical absorbers*, *fritted bubblers*, and *glass beaded columns*. The selection of an appropriate absorbing device depends upon the solubility and reactivity of the gaseous agent being collected.

Simple gas wash bottles such as the Greenberg-Smith (35)(37) and midget impinger (24)(52)(56)(63) are suitable for sample collection of nonreactive gases and vapors that are highly soluble in absorbing liquids and form near perfect solutions such as methanol in water and esters in alcohols. High collection efficiency can also be achieved by utilizing specific absorbing reagents which react rapidly with the gaseous contaminant, chemically changing it to a more stable form. Examples of these are 2,4-toluene diisocyanate (TDI) hydrolyzed by an absorbing reagent solution to a corresponding toluenediamine derivative (64), and p,p diphenylmethane diisocyanate (MDI) hydrolyzed to methylene dianiline (65).

The midget impinger (Figure I-3) has been the most widely used gas washing bottle for sampling of gases and vapors in the occupational environment. They can be used to collect general area air samples from a stationary position; they can be hand held to collect worker breathing zone samples; or they can be attached to the worker's clothing for a personal sample. A

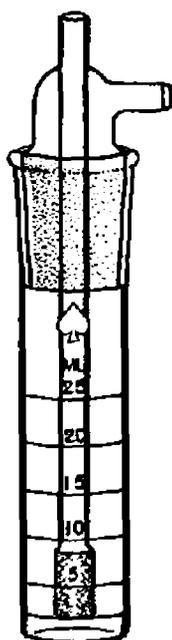


Figure I-3. Midget Impinger

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serious problem often encountered in the field is accidental spillage of the absorbent liquid by the worker bending over and inverting the impinger. However, spillproof impingers have been developed and are commercially available (38). The collection efficiency can be increased by entraining two or more impingers in series (25)(26).

Spiral Type Absorbers—(Figure I-4) are examples of gas wash bottles that can be used to collect gaseous substances that are only moderately soluble or slow reacting with reagents in the absorbing medium. These absorbers are essentially the same as those for simple gas wash bottles except that the spiral or helical structure design provides for higher collection efficiency by forcing the air sample to travel a spiral or helical path through the liquid. This takes five to ten times longer than does the simple wash bottle; allows a longer residence time within the tube; and results in longer contact between the sampled air and the absorbing solution.

Fritted Bubbler—(Figure I-5) are the most commonly used absorbing devices in the field today for sampling gaseous air contaminants in ambient work atmospheres. They are more efficient collectors than simple gas wash bottles

and can be used to collect gases and vapors that are only slightly soluble or reactive with the absorbing liquid medium. The principle involves drawing the air sample through a sintered or fritted glass bubbler which is submerged in an absorbing solution or reagent. As the sampled air is drawn through the fritted bubbler, many small bubbles and a heavy froth develop, increasing the surface area and contact time between the gaseous contaminant and the absorbing solution. Air bubble size is dependent upon the nature of the absorbing liquid and diameter of the orifices from which the bubbles emerge.

Frits are classified as fine, coarse, and extra coarse depending on the number of openings per unit area. Coarse frits are used when a rapid sample rate is desired and when the gaseous contaminant sampled is appreciably soluble and/or reactive in the absorbing liquid medium. Medium porosity frits are used for gases and vapors that are more difficult to collect, and fine porosity frits are used for highly volatile gaseous substances that are extremely difficult to collect. In general, smaller bubbles and greater generated froth effectuate greater surface area and contact

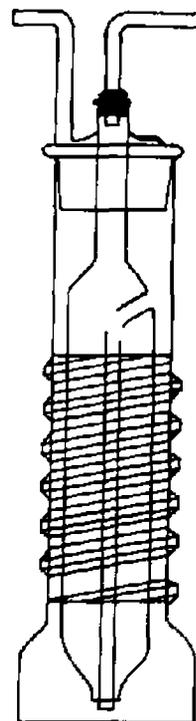


Figure I-4. Spiral Absorber

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time between the gaseous contaminant and the absorbing solution—hence, greater collection efficiency.

Columns packed with glass pearl beads (Figure I-6) coated with an appropriate absorbing medium are used in special situations where concentrated solutions of a gaseous contaminant is required. The beads provide a large surface area for collection of the gaseous contaminant. This absorption method has been used successfully in the past to collect benzene and other aromatic hydrocarbon vapors in nitric acid (91).

Adsorption

The most common air sampling method used today to collect trace quantities of insoluble or nonreactive gases and vapors in the workplace is adsorption with solid sorbents. Several solid sorbents have been successfully used such as activated alumina (11), molecular sieves (2) (11), porous polymer beads (22)(48)(59)(60), silica gel (16), and activated charcoal (28)(29) (30)(76) (93)(103)—with the latter two being the most widely used. The principle of adsorption involves drawing a known volume of air at a controlled flow rate through a small tube packed with an appropriate sorbent material. As the air passes through the tube, the molecules of the contaminant are adsorbed onto the surface of the sorbent chemically and physically unchanged. The contaminant is then desorbed (extracted) from the sorbent by a liquid solvent or thermal desorption for subsequent analysis.

Solvent desorption (28)(72)(76)(103) has been considered the standard method for sample recovery. However, the use of thermal desorption (22)(59)(82)(93) is becoming more widely used because the entire sample can be removed from the sorbent and analyzed at once, increasing the sensitivity of the analytical method.

The adsorbing properties of activated sorbents are entirely determined by the nature and extent of their surfaces and may be classified as either electrically polar or nonpolar (2).

The polar adsorbents have an affinity for polar as well as nonpolar molecules, but prefer polar substances, such as water vapor. Polar adsorbents such as silica gel can, therefore, be used either for short duration sampling of atmospheres that contain relatively high concentrations of contaminants or in atmospheres that are sufficiently low in moisture content so that the ad-

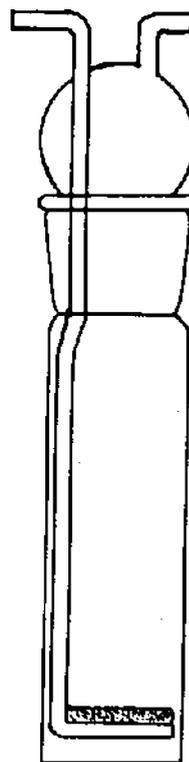


Figure I-5. Fritted Bubbler

Source: American Society for Testing and Materials: Tentative Method for Sampling Atmospheres for Analysis of Gases and Vapors. Philadelphia, July 24, 1956.

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sorbent does not become saturated with water vapor before sampling is complete (2).

Silica gel, an amorphous form of silica, is formed from reacting sodium silicate with sulfuric acid. It is electrically polar and therefore attracts partially charged (polar) molecules to active sites on its surfaces. Among the important advantages of using silica gel are: (1) desorption of contaminants can be easily accomplished with a variety of common solvents such as alcohols, ethers, and water; (2) it can be used to collect certain inorganic substances for which charcoal is unsuitable. A disadvantage is that being highly polar, water remains tightly bound to the surface of silica gel, and if sampling is continued long enough, moisture will displace relatively nonpolar organic solvents already collected. Beginning with water vapor, the descending order of polarizability of specific homologous chemical groups are: alcohols, aldehydes, ketones, esters, aromatic hydrocarbons, olefins,

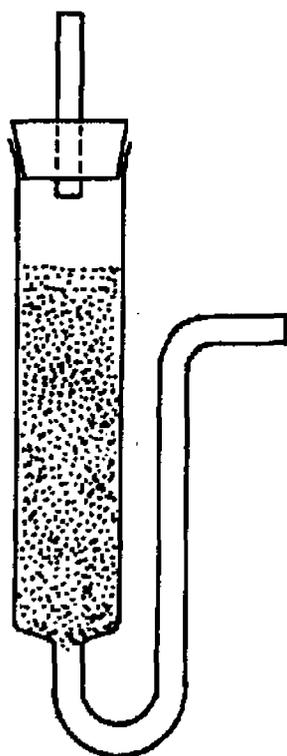


Figure I-6. Column packed with glass beads.

Source: American Society for Testing and Materials: Tentative method for Sampling Atmospheres for Analysis of Gases and Vapors. Philadelphia, July 24, 1956.

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and paraffins (78). Silica gel is currently the standard method recommended by NIOSH for aromatic (67) and aliphatic amines in air (66).

Charcoal (an amorphous form of carbon formed by burning wood, nutshells, animal bones, and other carbonaceous materials) is the most common solid sorbent in current use for sampling for airborne concentrations of organic solvent vapors. Because of its electrically non-polar character, it adsorbs organic vapors and gases in preference to atmospheric moisture.

The activated carbon currently recommended is coconut shell charcoal, manufactured to NIOSH specifications (11)(72). The advantage of using charcoal is that it has an extensive internal surface area, as large as 10,000 sq. ft. per gram of material (77), which greatly enhances its adsorption capacity.

Experience has shown that organic solvent vapors are usually encountered in the industrial environment as mixtures and not in a single pure form. Therefore, an air sampling and analytical

technique is desirable which is capable of collecting, separating, identifying, and determining the concentrations of each individual constituent of a mixture of airborne solvent vapors. The method that fulfills this requirement is the Charcoal Tube-Gas Chromatographic Method (28)(30)(56)(85)(86)(93)(103)(104)(Figure I-7). The method entails adsorption of organic vapors onto activated charcoal during sampling, desorption of the material from the charcoal with carbon disulfide, and subsequent analysis with flame ionization or electron capture gas chromatography. This is presently the air sampling and analytical method recommended for organic solvents in air by NIOSH (72).

Disadvantages of this method are that solvent desorption of the contaminant(s) from the charcoal is not always 100%, dilution of the sample occurs from solvent extraction resulting in a lowered sensitivity for analysis, and the carbon disulfide solvent used for desorption is extremely toxic and flammable.

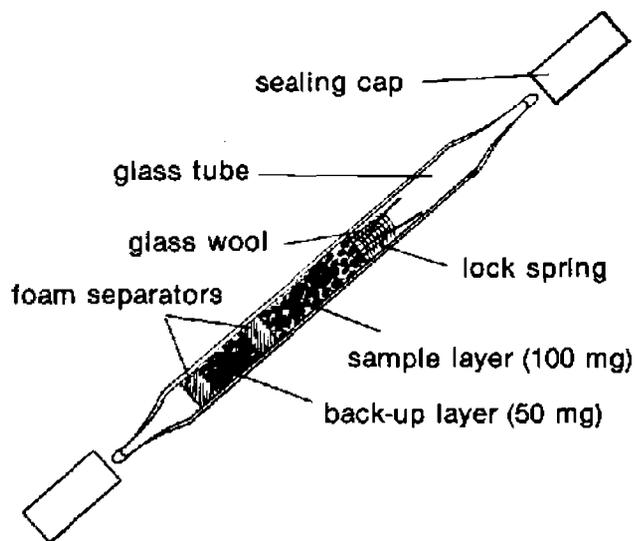


Figure I-7. Activated Charcoal Sampling Tube

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Inorganic compounds such as ozone, nitrogen dioxide, chlorine, hydrogen sulfide, and sulfur dioxide react chemically with activated charcoal and cannot be collected for analysis by this method (77). In addition, chemical substances such as the amines and particularly the aromatic amines (aniline, o-anisidine, p-anisi-

dine, N, N-dimethylaniline, p-nitroaniline, o-toluidine, and 2,4-xylidine) are not easily removed from charcoal and must be collected with other collecting media such as silica gel.

Impregnated Solid Sorbents—Until recently, the use of solid sorbents in air sampling has been restricted to the collection of nonpolar, insoluble, nonreactive gases. The development of ion chromatography (36)(97) as an analytical tool for the analysis of ionic forms of gaseous agents, and the subsequent development of solid sorbent tubes impregnated with absorbing reagents, has led to the successful collection and analysis of reactive (45)(71) and other gases (15) which previously could only be collected by wet impingement methods (71)(89) or for which no suitable method existed (62).

Any gas or vapor that can be quantitatively converted to an ionic form can be analyzed by ion chromatography. First, the sample is passed through an ion exchange column where the contaminant is retained. Second, the background ionic level of the eluent is suppressed by a second ion-exchange column which cancels the unwanted ions of eluent but does not affect the eluting ions. The eluting ions are detected by a conductivity detector.

The principle of sampling with impregnated solid sorbents involves the collection of a gaseous contaminant in standard solid sorbent tubes (69) impregnated with an appropriate absorbic reagent which changes the collected gas to a more stable ionic form. This is achieved by drawing the air through the sorbent tubes at a controlled flow rate for a known period of time. The sample is then desorbed with an appropriate solvent, followed by ion chromatography analysis.

Impregnated solid sorbent tubes using charcoal as the sorbent material, have been recently developed and tested for sulfur dioxide (96) and formaldehyde (45). These contaminants have traditionally been collected by wet chemical methods that require the use of liquid impingers. The overall recovery rates for sulfur dioxide and formaldehyde were reported as 94.6% and 100% respectively.

Impregnated solid sorbent tube sampling has significant advantages over the use of midget impingers. (1) It facilitates the collection and analysis of certain gaseous agents which do not lend themselves to more conventional methods; (2) the tubes are easily handled in the field; (3) they cannot be spilled; and (4) due to their small

size, they can be easily packed for safe transportation to the laboratory.

The combination of impregnated sorbent tubes and ion chromatography promises superior sampling and analytical methods for the collection and analysis of reactive gases and vapors. Further developmental work on impregnated solid sorbent tubes should result in tubes designed specifically for reactive gases such as ozone, nitrogen dioxide, chlorine, and hydrogen sulfide, as well as other inorganic and organic gases and vapors. Not only will sampling be simplified, but the analytical method itself will be more precise, accurate, and less expensive than most of the currently available methods.

Passive Dosimeters—Passive dosimetry is a new and innovative concept for sampling both organic and inorganic vapors that promises a simpler sampling future for the industrial hygienist. The method requires no air sampling pump, has a low unit and capital cost, can be used to monitor organic vapors currently being sampled by solid sorbent tube methods, and the samples can be analyzed using standard GC techniques. Inorganic vapors such as NO₂, SO₂, and NH₃ can be determined using the passive dosimeter in combination with photometry, chromatography, or colorimetry. The passive dosimeters produce an integrated sample for periods as low as 15 minutes and as long as 8 hours.

The process of passive dosimetry is based on Fick's first law of diffusion. The basic requirement is that complete collection efficiency occurs such that the concentration of contaminant at the collection surface is zero. The concentration of contaminant at the badge face is the ambient concentration. This results in a concentration gradient through which contaminant molecules diffuse at a constant rate.

Two mechanisms exist for collection of contaminant material. One is adsorption of the contaminant into a bed of uncoated solid sorbent such as charcoal or silica gel. The other method is to react the contaminant with a chemical coating on the collection surface. Both methods are currently used, with charcoal being used for nonpolar organics, silica gel for polar gases, and chemical coatings for reactive gases.

Development of dosimeters for NO_x and NO₂ (Figure 1-8) has been carried out primarily by Palmes et al. (79)(80)(81). Field tests of two types of NO₂ dosimeters have been conducted by Jones et al. (41). Evaluation of passive dosi-

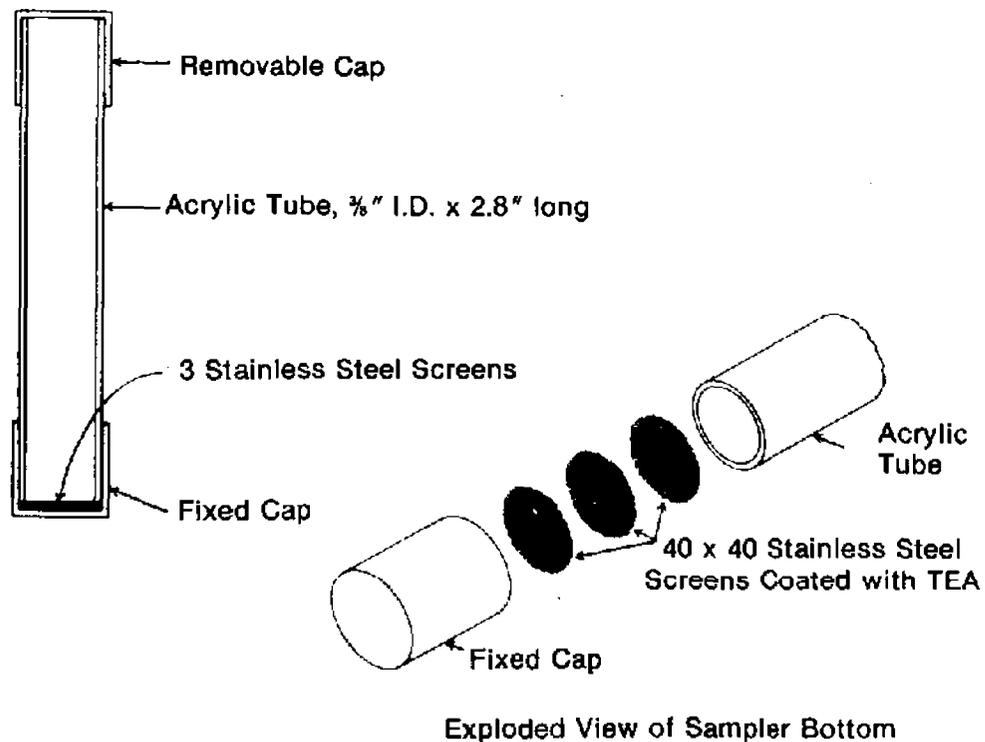


Figure I-8. Palmes Passive NO₂ Dosimeter

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meters for organic vapors have been conducted by Bamberger (13).

Commercial versions of the passive dosimeter have only recently begun to appear on the market. The industrial hygiene community has not yet had time to gain sufficient field experience in their use to fully evaluate the devices. However, the advantages of passive dosimeters are such that a great deal of effort is currently being put into their development and field evaluation.

Passive dosimeters are commercially available for SO₂ (99), NO₂ (99), mercury vapor (57), and aniline vapors (18), as well as several other gases (46)(49). The dosimeters are desorbed and analyzed by standard gas chromatography or other analytic methods.

A recently developed device which is now commercially available is a colorimetric air monitoring badge system. This system combines the passive dosimeter with colorimetry to quickly determine the time-weighted-average exposure of workers to SO₂, NO₂, NH₃, and HCHO (46).

The badge (Photograph 1) is exposed to the atmosphere for an appropriate length of time after which plastic blister packs containing chemical reagents are ruptured. The chemicals are mixed by palpating the plastic pack after which the concentration in parts per million hours is read from a portable colorimeter.

Another new passive dosimeter which is commercially available is an organic vapor air monitoring badge (Photograph 2) which features a backup section. The backup section serves the same purpose as the backup section in the standard charcoal tube, i.e., to determine whether or not breakthrough of contaminant from the front section has occurred. This device employs activated charcoal as a solid sorbent. Analysis is performed by gas chromatography just as with charcoal sampling tubes.

Condensation

The condensation method of sampling for gaseous agents is used to collect gaseous materials in liquid or solid form, primarily for



Photograph 1. Colorimetric Air-Monitoring Badge

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Photograph 2. Organic Vapor Air-Monitoring Badge with Back-up Section

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identification purposes (77), or to sample for gaseous contaminants (such as sulfur trioxide vapor) which are difficult to collect by other techniques (8). Samples are collected by drawing the air sample through a single or series of cold traps immersed in dry ice and acetone, liquid air, or in a liquid nitrogen refrigerant bath cooling system. The collection traps are of double-wall construction, with the sampled air passing through the space between the walls. Apparatus and procedures for condensation sampling have been previously described in detail (94).

To condense a given gas or vapor, the refrigerant should be cold enough to reduce the temperature of the substance below its boiling point and maintain the vapor pressure of the trapped material sufficiently low to prevent significant evaporation during the sampling period. Generally, the vapor pressure should be about 1 mm of mercury or lower at the cold trap temperature (42). Condensation methods have the advantage of concentrating contaminant gases or vapors and preserving them in their natural state, without a chemical reaction. This method is particularly useful when airborne concentrations of a given gaseous contaminant are low and a highly concentrated sample of the material is required for analysis. An important disadvantage of the condensation method is that the condensation unit is somewhat bulky and not considered to be a portable field instrument. Other special problems are that unwanted substances in the air sample will also condense out, often in copious quantities, such as water vapor, hydrocarbons, and other gaseous contaminants that readily condense to the liquid state at temperatures of ice water. Although a compact condensation method has been developed (51), the disadvantages inherent in this method have relegated its use to a last resort status.

DIRECT READING INSTRUMENTATION

Portable direct reading instrumentation designed to detect and measure worker exposure to airborne concentrations of *particulates* and *gases* and *vapors* has undergone significant evolution within the past decade (1970's), primarily due to the passage of the Federal Occupational Safety and Health Act of 1970, which requires each employer to provide a safe and healthy workplace. The safety and health standards promulgated under this legislation provide

an economic incentive for the commercial production of more sophisticated and accurate direct reading instrumentation, with the capability to immediately detect and measure potentially hazardous concentrations of airborne contaminants.

Direct reading instrumentations are of two general groups. The first group consists of those that produce a *color change* either in solution or detector (indicator) tubes through which the air sample has been drawn or on chemically treated papers exposed to contaminated atmospheres. The second comprises those that have *electronic circuitry* and are capable of sampling a volume of air, performing qualitative and/or quantitative analysis internally, and displaying the results immediately on a dial, illuminated digital display panel, tape printout, or strip chart recorder.

Colorimetric Direct Reading Indicators

There are essentially three types of direct reading colorimetric indicator systems used for the determination of concentrations of gaseous contaminants in air: *liquid reagents*, *chemically treated papers*, and *detector tubes* (also called indicator tubes). Detector tubes contain solid supports treated with chemical reagents. All three systems utilize the chemical properties of an atmospheric contaminant to produce a reaction with a color-productive reagent (44). Comprehensive bibliographies on this subject have been previously prepared (17)(88).

Chemical indicators primarily lend themselves to the detection and semiquantitative analysis of airborne gaseous contaminants. Their accuracy depends largely on the care with which the given type of indicator (detector) system is prepared and standardized. Among the most important considerations are the experience of the operator and his knowledge of the atmosphere being sampled. By knowing the limitations of the chemical reaction and having a general idea of the atmosphere being sampled, a relatively quick and inexpensive estimate of the agent of interest may be obtained.

Liquid Reagents

Here the reagent solution is carried into the field with an air sampling unit such as a liquid impinger or bubbler (9)(71)(89). In this inconvenient but sensitive procedure (often referred

to as "air titration" or "air colorimetry"), the reagent or scrubbing solution must trap and react with the contaminant to either produce a color change from which a semiquantitative analysis is made, or the colorless reagent is returned to the laboratory for analysis (73).

Field use of liquid reagent sampling is more prevalent than the literature indicates because many laboratories have taken routine procedures and made reference solutions for direct comparison with the field sample for concentration determinations.

The use of Saltzman's reagent (80)(90) in a fritted glass bubbler to determine the ambient airborne concentrations of oxides of nitrogen has been a classic application of this method. A known titer and volume of Saltzman's reagent is placed in an all glass bubbler connected to an air pump with a length of tubing. The contaminated air is pulled through the reagent in a bubbler at a controlled rate until a perceptible color change occurs. The concentration of nitrogen dioxide in air is inversely proportional to the time required to produce a perceptible color change.

A disadvantage of liquid methods in the field is that they are inconvenient and bulky to transport. An important advantage is that the measurement of color in liquids is inherently more reproducible and accurate than the measure of color on solids.

Chemically Treated Papers

Although rarely used today because of the availability of more sophisticated, sensitive, and accurate methods, paper impregnated with chemical reagents found wide application for many years in the detection of toxic gases and vapors in work atmospheres. Examples are papers impregnated with mercuric bromide for the detection of arsine, lead acetate for the detection of hydrogen sulfide, a mixture of o-toluidine and cupric acetate for the detection of hydrogen cyanide (44), and detector tabs for carbon monoxide (58). The observed time required for a color change after exposure of a specific paper or tab to an agent is an indication of the concentration present. Other examples are chemical chalks and crayons formulated for use in sensitizing paper (40)(105) to phosgene, hydrogen cyanide, cyanogen chloride, and Lewisite (dichloro(2-chlorovinyl)arsine). Chalks, crayons, and chemically treated papers can be found in

military chemical warfare field surveillance sets today.

Detector Tubes

First developed in 1917 at Harvard University (3), the detector (or indicator) tube has been widely used in recent years as a useful, convenient, and economical tool for the detection and semiquantitative estimation of potentially toxic gaseous agents in industrial atmospheres.

Developed first for carbon monoxide, the methodology of these colorimetric indicator tubes has progressed to include a wide variety of tubes. Until World War II, the only indicator tubes in general use by industrial hygienists were for hydrogen sulfide and carbon monoxide (27). Presently, there are detector tubes for nearly 200 atmospheric gases available from four major companies and manufacturers.

A detector tube unit is composed of a pump, a colorimetric indicator tube, and possibly a conditioning tube. The preferred pump is either a bellows or a positive displacement piston type pump designed to draw a fixed volume of air with each stroke. Squeeze bulb-type pumps are no longer recommended because of reproducibility problems with the air volume drawn.

The indicator tube is a hermetically sealed glass tube containing a granular material such as silica gel, alumina, or pumice impregnated with a chemical reagent that reacts with the contaminant in the airstream as it is drawn through the tube.

To conduct a test, the two sealed ends of the indicator tube are broken off and the specified end of the tube is inserted into the rubber septum inlet of the pump after which a fixed volume of air is drawn at a controlled rate through the tube. After a short specified time has been allowed for color development, the concentration is determined. This is accomplished in one of three ways depending on the type of detector tube system used: 1) by comparing either an absolute length of stain produced in the column of indicator gel or a ratio of the stain length to the total gel length against a calibration chart to obtain an indication of the atmospheric concentration of the contaminant; 2) by comparing a progressive change in color intensity with a chart of color tints; or 3) noting the time required to produce an immediate color change in which the air volume sampled is in-

tended to be inversely proportional to the concentration of the atmospheric contaminant.

The results obtained from matching tube color change with charts of color tint is highly subjective among readers. The visual judgment, among other things, is dependent on the color vision of the readers and the quality of lighting in the immediate area. To reduce this source of reader error, the most recent types of tubes are based on the production of a variable length of stain on the indicator gel.

Another source of error is temperature. Because the chemical reaction rate is dependent on temperature, it should be recognized that many tubes will give erroneous readings at high or low temperatures.

Because of their simplicity and ease of operation, indicator tubes are widely advertised as being capable of use by unskilled personnel to rapidly assess worker exposure to potentially hazardous levels of toxic gases and vapors. While it is true that the operating procedures are simple, rapid, and convenient, it has been repeatedly demonstrated in practice that serious errors in sampler operation, in selection of sampling locations and times, and in the interpretation of results can occur unless the instrument is in the hands of a well trained operator who is supervised by a competent health professional. A manual describing recommended practice for colorimetric indicator tubes, published by the American Industrial Hygiene Association, explicates the principles of operation, applications, and limitations of these devices (3).

Perhaps the most difficult problem associated with the use of indicator tubes is that of interfering gases. The problem primarily lies in the use of indicating reagents which lack specificity. For example, the use of a hexavalent chromium compound as a tube reagent to oxidize a number of organic substances (which produce a given chromatic color reaction) is non-specific (44). All readily oxidizable substances may affect the indication. Also, aromatic hydrocarbons, halides, hydrides, and chlorinated hydrocarbons are chemicals widely used in industry and often found as mixtures in air. These are examples of class compounds for which single reagent formulations in detector tubes have been used. A single reagent formulation limits the usefulness of these tubes in mixed exposure areas, since several gases are present and the tube can give only one reading. Additionally, two or more gases can interfere with each other

during the color-producing reaction. However, the single reagent formulations can still be useful in estimating maximum worker exposure because almost all interferers increase the stain length.

Historically, there have been and still are serious problems with tube quality due to a lack of quality control among manufacturers. Rigid quality control of reagent(s) purity, grain size of supporting material, method of packing tubes, moisture content, uniformity of tube diameter, and proper storage precautions are required for optimal and consistent performance of any detector tube. The most critical problem is that there are few standardized methods for generating known concentrations of calibration gases for these tubes. The use of detector tubes that are produced with poor quality control and that have questionable performance requirements could result in an occupationally hazardous situation remaining unrecognized or uncorrected.

A move was made in 1973 to rectify this problem by the issuance of regulations for certification of gas detector tube units. These regulations appeared in the Federal Register on May 8, 1973, (38FR 11458) and were incorporated in the Code of Federal Regulations as Title 42 CFR Part 84 under authority of the Occupational Safety and Health Act of 1970. However, in 1978, HEW withdrew these regulations since they were no longer federally mandated, but certification continued under the National Institute for Occupational Safety and Health's (NIOSH) Guidelines.

Performance requirements for gas detector units were also developed by NIOSH, with the cooperation and assistance of members of the Joint Direct Reading Gas Detecting Systems Committee of the American Industrial Hygiene Association and American Conference of Governmental Industrial Hygienists.

NIOSH certifies a manufacturer to produce a gas detector tube unit to meet the minimum requirements set forth in the NIOSH Guidelines (basically $\pm 35\%$ accuracy at $\frac{1}{2}$ the exposure limit and $\pm 25\%$ at 1 to 5 times the exposure limit). The quality of future production lots is evidenced by a quality assurance plan which NIOSH approves as part of the certification. Adherence to the quality assurance plan is verified by periodic plant inspections and by testing samples purchased on the open market.

As of July 1980, NIOSH had issued certifications for 63 gas detector tube units from 5

Table I-37
NIOSH CERTIFIED GAS DETECTOR TUBE UNITS

Calibrated for	Certification	Manufacturer	Model Tube/Pump(s)
Acetone	*TC-84-054	MSA	460423/83499 or 463998
Ammonia	*TC-84-023	Gastec	3M/400
Ammonia	*TC-84-031	Drager	CH20501/31
Ammonia	*TC-84-032	Kitagawa	105Sc/400
Ammonia	*TC-84-033	Kitagawa	105c/400
Ammonia	*TC-84-034	MSA	460103/83499 or 463998
Benzene (A)	*TC-84-043	Gastec	121/400
Benzene (A)	*TC-84-044	Drager	67-28071/31
Carbon Dioxide	TC-84-021	Gastec	2L/400
Carbon Dioxide	TC-84-025	MSA	85976/83499 or 463998
Carbon Dioxide	TC-84-026	Kitagawa	126Sa/400
Carbon Dioxide	TC-84-027	Kitagawa	126a/400
Carbon Dioxide	TC-84-029	Drager	CH23501/31
Carbon Disulfide	*TC-84-066	Drager	67-28071/31
Carbon Monoxide (A)	TC-84-012	Drager	CH25601/31
Carbon Monoxide (A)	TC-84-013	Drager	CH20601/31
Carbon Monoxide (A)	TC-84-014	Gastec	1La/400
Carbon Monoxide (A)	TC-84-015	MSA	91229/83499 or 463998
Carbon Monoxide (A)	TC-84-019	Kitagawa	106S/400
Carbon Monoxide (A)	TC-84-045	Kitagawa	100/400
Carbon Monoxide (A)	TC-84-067	MSA	465519/83499 or 463998
Carbon Monoxide (B)	TC-84-013	Drager	CH20601/31
Carbon Monoxide (B)	TC-84-067	MSA	465519/83499 or 463998
Carbon Tetrachloride	TC-84-036	Gastec	134/400
Chlorine	*TC-84-041	Gastec	8La/400
Chlorine	*TC-84-042	MSA	460225/83499
Chlorine	*TC-84-070	Drager	67-28411/31
Ethyl Benzene	*TC-84-064	Drager	67-28381/31
Ethylene Dichloride	*TC-84-058	MSA	461863/83499 or 463998
Hexane (normal)	*TC-84-063	Drager	67-28391/31
Hydrogen Chloride	TC-84-071	Drager	CH29501/31
Hydrogen Cyanide	TC-84-051	Drager	CH25701/31
Hydrogen Cyanide	*TC-84-052	Kitagawa	112Sb/400
Hydrogen Cyanide	*TC-84-068	Gastec	12L/400
Hydrogen Sulfide (A)	TC-84-020	Gastec	4LL/400
Hydrogen Sulfide (A)	TC-84-022	MSA	460058/83499 or 463998
Hydrogen Sulfide (A)	TC-84-024	Drager	67-19001/31
Hydrogen Sulfide (A)	TC-84-037	Kitagawa	120b/400
Hydrogen Sulfide (B)	TC-84-062	Drager	CH29801/31
Hydrogen Sulfide (B)	TC-84-072	MSA	463875/83499 or 463998
Methyl Bromide	*TC-84-056	Drager	67-28211/31
Methylene Chloride	*TC-84-061	Drager	67-28331/31
Nitric Oxide	*TC-84-048	Drager	CH31001/31
Nitric Oxide	*TC-84-049	Gastec	10/400
Nitric Oxide	*TC-84-059	MSA	460424/83499 or 463998
Nitrogen Dioxide	*TC-84-016	Drager	CH30001/31
Nitrogen Dioxide	*TC-84-018	Gastec	9L/400
Nitrogen Dioxide	*TC-84-040	MSA	83900/83499 or 463998

Table I-37
NIOSH CERTIFIED GAS DETECTOR TUBE UNITS (Continued)

Calibrated for	Certification	Manufacturer	Model Tube/Pump(s)
Nitrogen Dioxide	*TC-84-048	Drager	CH31001/31
Perchloroethylene	*TC-84-065	MSA	460467/83499 or 463998
Sulfur Dioxide	*TC-84-017	Gastec	5La/400
Sulfur Dioxide	TC-84-028	Kitagawa	103Sd/400
Sulfur Dioxide	TC-84-030	Drager	CH31701/31
Sulfur Dioxide	TC-84-035	Kitagawa	103d/400
Sulfur Dioxide	TC-84-046	MSA	92623/83499 or 463998
Sulfur Dioxide	TC-84-069	Drager	67-28491/31
Toluene	TC-84-050	Drager	CH23001/31
Toluene	TC-84-053	Gastec	122/400
Toluene	TC-84-057	MSA	461371/83499 or 463998
Trichloroethylene	TC-84-038	Gastec	132H/400
Trichloroethylene	TC-84-039	Drager	CH24401/31
Trichloroethylene	TC-84-055	MSA	460328/83499 or 463998
Vinyl Chloride	TC-84-060	Gastec	131L/400

*The unit indicates a general class of compounds (amines, hydrocarbons, strong oxidents, etc.) to differing degrees. The calibration is certified only for the compound listed.

The above includes all the gas detector tube units certified by NIOSH through July 1, 1980. The units are sorted by the gas for which they are certified. Some gases contain more than one testing range and are listed more than once with "Range A" or "Range B" immediately following the gas name.

manufacturers (68)(2) (see Table I-37). While the certified units represent the bulk volume sold in the United States, they are certified to measure only 23 gases.

Long-Term Detector Tubes

The successful development and use of the detector tube as an instrument for rapid detection and semi-quantitative determination of worker exposure to gaseous contaminants has led to the development of long-term detector tubes which can sample work atmospheres over an extended period of time (up to 8-hours) to measure the worker's integrated or time-weighted-average exposure.

Long-term detector tubes (LTT) are similar to short-term detector tubes in both physical appearance, method of detection, and display of a contaminant's concentration. Long-term detector tube samples are acquired by drawing the air through the tube at a controlled low flow rate with a battery powered pump.

A color change occurs in the LTT when the air sample contains the gas or vapor to which the tube is sensitive. The tube has been calibrated and marked by the manufacturer, allowing the amount of contaminant to be determined by

reading the length of stain and making a simple calculation.

Most long-term tubes can sample continuously for periods up to 8 hours; short-term tubes typically sample only ½ to 5 minutes. The flow rate through an LTT is usually a low constant—5 to 20 ml/minute. A short-term tube has a flow rate that varies with the elapsed time, measured from the time the hand pump is released. Short-term tubes are very sensitive to flow rate and must be used with the specific pump recommended by the manufacturer. LTT's seem to be usable with any low flow pump, as long as the flow rate is constant and within the range recommended by the manufacturer (43).

The LTT and pump can be worn by the worker as he goes about his regular routine. At the end of the sampling period the tube can be read and the worker's exposure for that day recorded as part of his occupational work history.

With the LTT, only the worker's time-weighted-average exposure is reflected. To acquire an indication of the concentration of a gas over a short interval of time, the short-term detector tube is used. To measure peak concentrations, as required in determining compliance or non-compliance with short-term exposure limits and

ceiling values, electronic direct-reading instruments equipped with a strip chart recorder are used.

There are currently three manufacturers of long-term detector tubes; National/Drager, Mine Safety Appliances, and Kitagawa. The tubes are new to the industrial hygiene community and have not yet been critically evaluated.

Detector tubes have a valuable place in the arsenal of air sampling instrumentation used to detect worker exposure to potentially harmful gases and vapors. Their usefulness will ultimately depend on the quality with which they are produced and the knowledge and good judgment with which they are used. Some mechanism must be derived to provide occupational safety and health professionals with quality detector tubes for rapidly detecting a wider spectrum of toxic gases and vapors to which workers may be exposed in occupational environments. Following a recent study of the NIOSH Certification Program conducted by a team of highly qualified consultants from several professional disciplines, formal recommendations were presented in an interim report regarding the future role NIOSH should play in the testing and certification of hazard measuring instruments (70).

Electronic Direct Reading Instrumentation

The rapid development of portable and sensitive electronic direct reading instrumentation for evaluating workroom atmospheres has largely been due to the borrowing of air sampling and analysis technology already developed in the disciplines of radiation protection and air pollution control.

This class of direct reading instruments incorporates electronic sensors utilizing infrared and ultraviolet radiation, flame and photoionization, and chemiluminescence capable of detecting and measuring airborne concentrations of gases and vapors in a matter of seconds. Most of these instruments can be equipped with automatic continuous recording devices which generate real time data (representing peak exposure concentrations at any point in time) as well as time weighted data (averaging concentrations over time from a few seconds or minutes to full 8-hour work periods or longer), depending on the kind of exposure information required.

Among the most innovative improvements in electronic direct reading equipment has been

the recent mating of electronic direct instrumentation with microcomputers. Advances in microprocessor technology allow computerized instrument versions to retain the size and technical features of the previous versions in addition to having the control and mathematical capabilities of a microcomputer based system. Among the important functions the computerized version can accomplish are: immediate treatment and reduction of a mass of exposure data to a readily usable form upon termination of sampling, correction of interferences, and depending upon the capability of the basic instrument, automatic analysis for multi-component mixtures.

The operating principles of direct reading instrumentation are based upon the physical and/or chemical properties of the gaseous agents they detect and quantify. As a group, these principles are based on two phenomena:

The first is the *physical principle* in which the electronic detector or sensor element that generates the electrical signal with its information content is immediate to the air sampling process. A classic example is the mercury vapor meter where the principle involved is the absorption of ultraviolet (UV) light by mercury vapor which has a strong absorption line in the 253.7 millimicron region of the UV spectrum. The instrument consists of an absorption chamber, with a UV light source located on one end of the chamber and a photosensitive detector/sensor element located on the other. A sample of the immediate atmosphere being monitored is drawn through the instrument's absorption chamber where the UV light is absorbed by mercury vapor present in the airstream. The presence of the mercury vapor reduces the UV radiation reaching the photosensitive detector element in proportion to the concentration present. The change in intensity of UV radiation reaching the photosensitive detector element, which is connected to one arm of a Wheatstone bridge, creates an unbalanced condition that is detected and displayed on a meter as mercury vapor concentration in terms of milligrams of mercury per cubic meter of air (mg/m^3).

The second is the *chemicophysical principle*, in which the gas or vapor undergoes a chemical reaction, and a physical method is used to detect the changes caused by this reaction. Either the consumption of one of the reactants or the production of a product is measured. In either case, a physical property of a reactant or of a product

is measured. Oxidation-reduction reactions are typical examples of chemico-physical detection methods. The chemical part of the method is the oxidation or reduction of the contaminant; the physical part is a measurement of the number of electrons required to regenerate one of the reactants.

The Mast ozone meter employs a chemico-physical method of detection. Ozone (O₃) is used to oxidize potassium iodine to molecular iodine and potassium hydroxide. The free iodine produced reacts with a thin hydrogen layer that covers a wire electrode. This reaction consumes both hydrogen and iodine to yield hydrogen iodide. The removal of the thin layer of hydrogen allows a polarization current to flow through the wire, regenerating the thin hydrogen layer. For each ozone molecule in the sample, two electrons flow in the circuit. The microcoulomb sensor counts these electrons and displays the concentration of ozone in parts per million (ppm).

The scope and intent of this section does not lend itself to a comprehensive survey of existing electronic direct reading instrumentation. Rather, it delineates how chemical and physical properties of gaseous materials, together with detection methods and various performance parameters can be used to select a specific instrument to measure a given gas. Table I-38 lists methods of detection for agents causing occupational respiratory disease (ORD). Table I-39 lists the methods of detection, the chemical species to which the detector is sensitive, and a brief description of the principle of detection. Table I-40 lists the performance criteria upon which the various instruments can be evaluated and a description of the criteria.

For an excellent work describing most of the direct reading as well as nondirect reading air sampling instrumentation, the reader is referred to a publication by the American Conference of Government Industrial Hygienists (1).

Table I-38

MAJOR METHODS OF DETECTION FOR COMMON AGENTS CAUSING ORD.

X indicates the existence of a commercially available instrument employing the listed method of detection.

Detector	Agents									
	NH ₃	Cl ₂	NO _x	SO _x	O ₃	COCl ₂	Hg	H ₂ S	C*	S**
Flame Photometric				X						
Chemiluminescence			X		X					
Colorimetry	X		X	X						
Coulometry				X	X					
Electrical										
Conductivity	X			X			X			
Flame Ionization									X	
IR Photometry			X							
Photoionization									X	X
Derivative										
Spectrometry	X		X	X					X	X
Thermal										
Conductivity		X	X	X		X		X		
Voltammetric								X		
Electro										
Chemical		X	X	X	X	X				
Microcoulomb										
Redox			X							

Table I-38

MAJOR METHODS OF DETECTION FOR COMMON AGENTS CAUSING ORD. (Continued)

X indicates the existence of a commercially available instrument employing the listed method of detection.

Detector	NH ₃	Cl ₂	NO _x	SO _x	Agents		Hg	H ₂ S	C*	S**
					O ₃	COCl ₂				
Mass Spectrometry						X				
Electron Impact Spectrometry			X	X						
Electron Capture			X							
UV Photometry		X	X			X	X	X	X	X

*Carbon containing ORD agents.

**Sulfur containing ORD agents.

Table I-39
DETECTORS*

Method of Detection	Gas or Vapor Detected	Description of Detector
Flame photometric	Sulfur compounds	When a sulfur compound is burned in a hydrogen flame, energy at a wavelength of 394 nanometers is emitted. This energy is detected by a (UV) photometer and related to the concentration of the sulfur compound through a calibration curve. This curve plots contamination concentration along the X-axis and light intensity along the Y-axis.
Chemiluminescence	O ₃ NO/NO _x	When a molecule is excited to an unstable state (higher energy) and allowed to decay to a more stable (lower energy) state, a photon of energy is emitted within a specific wavelength range. The intensity of the emitted energy is related to the concentration of the excited molecule.
Colorimetry	SO ₂ NO ₂ NO _x NH ₃ Cl ₂ HCN	Certain gases can react with liquid color producing reagents that quantitatively convert the gas or the reagent to a colored liquid. The intensity of the color is related to the concentration of the contaminant gas. The intensity is measured using a visible light photometer set at the appropriate wavelength.
Coulometry	O ₃ SO ₂ NO ₂ NO CO H ₂ S	The consumption of electrons by a chemical reaction is measured using a microcoulomb sensor. One microcoulomb equivalent is the number of electrons required to reduce a mass of water on the order of nanograms. A microcoulomb is defined as a current of one micro-ampere flowing for one second.

Table I-39
DETECTORS* (Continued)

Method of Detection	Gas or Vapor Detected	Description of Detector
Electrical conductivity	NH ₃ H ₂ S SO ₂	Gases that ionize in aqueous solution change the resistance of the solution to the flow of electrons. The more ions present in the solution, the greater the electron flow at a constant potential difference. This method of detection is nonspecific, i.e., the electrical conductance depends only on the number of ions present and not on the type of ions.
Flame ionization	Any volatile hydrocarbon	A gas is burned in a hydrogen flame, producing a large number of ionic fragments. These ions flow to a collection electrode where they are counted electronically. The method is nonspecific, responding to any hydrocarbon.
Photometry, IR	Hetroatomic gases CO N ₂ O NO NO ₂ CH ₄ SO ₂ C ₂ H ₄ Ammonia 2-Butonone CS ₂ CO ₂ CO CCl ₄ Chloroform Dimethyl formamide Ethylene oxide Methylene chloride Styrene Toluene Trichloroethylene	Infrared radiation produced by two hot filament sources passes through two parallel tubes—one a reference cell containing only pure air; the other a sample cell containing the contaminated air. The contaminant absorbs (at its absorbing wavelength) some of the IR radiation. The difference in the percent transmittance between the two cells is related to the concentration of the contaminant. This method is somewhat specific, depending on the wavelength selected and the other constituents of the sample.
Photoionization	Xylene Benzene Toluene Diethyl sulfide Diethyl amine Styrene Trichloroethylene CS ₂ Acerone Tetrahydroforan Methyl ethyl ketone	The ionization potential of a molecule is measured in electron volts (ev). If light energy greater than the ionization potential of a given gas is passed through the gas, a certain percentage of the molecules will ionize by absorbing the energy. The ions produced are collected, counted, and related to the concentration of the contaminated gas.

Table I-39
DETECTORS* (Continued)

Method of Detection	Gas or Vapor Detected	Description of Detector
	Aromatics (naphtha) Vinyl chloride Methyl mercaptan	
Derivative spectrometry	NO ₂ NO SO ₂ NH Cl ₂ O ₃ Naphthalene Pyrroline Others...	This method relates the rate of change in a gas' energy absorption to the wavelength at which the absorption is being measured. The first to n th derivative of the absorption equation is plotted along the Y-axis, and the concentration in PPM's along the X-axis. The rate of change in absorption as the wavelength changes is more sensitive to small changes in the concentration of the absorbing gas than the absorption equations up to a factor of 10.
Thermal conductivity	H ₂ He O ₂ N ₂ CO CO ₂ CH ₄ Ethane C ₁ to C ₂ hydrocarbons Alcohols Aromatics NH ₃ Cl ₂ H ₂ S N ₂ O CO ₂	A wire is heated by passing a current through it. The current is such that the rate of heat transferred from the wire to a carrier gas stream passing over the wire is just equal to the amount of heat produced by the constant current through the wire. This leaves the temperature of the wire constant, and at a constant temperature, the resistance to electron flow is constant. Different gases have specific heats of conductance. If a gaseous contaminant is injected into the carrier gas stream, the amount of heat transferred from the wire will change. This results in a change in the wire temperature and resistance to electron flow through the wire. The change in resistance is measured and related to contaminant concentration.
Voltammetric	CO 10,50,100,600 SO ₂ H ₂ S	A potential difference is maintained between a sensing and a reference electrode. The gas molecules are the current carrying elements, linking the two electrodes together. As the ionic or partially charged molecules migrate to the sensing electrode, a small current flows through the system. This current is related to the concentration of the contaminant gas.
Electrochemical	SO ₂ H ₂ S Mercaptans Thiophene Organic sulfides	Gas molecules are absorbed on an electrode, where they are oxidized or reduced (depending on the gas) at a given potential difference between the electrode and a measuring electrode. The number of electrons required to complete

Table I-39
DETECTORS* (Continued)

Method of Detection	Gas or Vapor Detected	Description of Detector
	Disulfides Vinyl chloride CO Combustible Gases Cl ₂ NO NO _x	the redox reaction is related to the concentration of the contaminant gas.
Microcoulomb redox	O ₃ NO ₂	Similar to the voltammetric and the electrochemical methods.
Mass spectrometry	CO CO ₂ NO NO ₂ N ₂ O SO ₂ O ₃ Hydrocarbons	When a molecule is fragmented, a variety of ions are formed. If these ions are entrapped in a flow of carrier gas and subjected to a magnetic field perpendicular to the flow, the ions will be deflected from their normal flight path. The degree of deflection will depend on the charge to mass ratio of the ionic fragments. Mass spectrometry requires a very small sample size, usually a few microliters of the gas. The method is highly specific and can be combined with gas chromatography for even greater specificity.
Electron impact spectrometry	SO ₂ NO CO CH ₄	An electron beam causes the molecules to emit energy in specific wavelength ranges. This energy is collected and measured by the detector.
Electron capture	SF ₆ CCl ₄ Freon	A radioactive source ionizes some molecules in the carrier gas stream producing a constant current. When the sample gas passes through the sample cell, it absorbs some of the electrons, causing the signal to change.
Gas chromatography		
Electron capture	See Table I-37	A method of separating a mixture of two or more gases based on the solubility coefficient of the gas in various mediums.
Flame ionization	See Table I-37	
Flame photometric	See Table I-37	
Thermal conductivity	See Table I-37	
Photometry, UV	Mercury vapor Halides O ₃ SO ₂ NO ₂	

*Specific instruments employing a given method can be found in *Air Sampling Instruments for Evaluation of Atmospheric Contaminants* (1).

Table I-40
CRITERIA FOR INSTRUMENT EVALUATION

Criteria	Description
Accuracy	Accuracy refers to how close to the true atmosphere gas or vapor concentration the instrument reads. The true value can be determined by use of an accepted primary standard or a reference measurement. Accuracy can be stated as a percentage deviation from the true value.
Calibration	Calibration refers to the establishment of a direct correspondence between the instrument reading and the sample concentration. Once calibrated, an instrument must be periodically checked to verify that it is still within an acceptable calibration range. Unstable instruments (subject to poor reproducibility, temperature, and zero drift) require frequent calibration.
Interference	<p>Interference refers to instrument response to anything other than the gas or vapor being measured. The instrument may give either a higher or lower reading than would be produced by the true pollutant concentration acting on the sensor alone.</p> <p>The industrial hygienist must be aware of all possible sources of interference to the instrument employed. Appropriate precautions and corrections must be made for interferences.</p>
Noise	Noise refers to spontaneous, spurious changes in the instrument output signal that are unrelated to the concentration of the gas or vapor being studied. Noise originates in the electronic components of the system.
Precision	Precision refers to the repeatability of instrument response to the same gas or vapor concentration over a period of time. Repeated measurements are taken, and a mean and a standard deviation are calculated. A large standard deviation relative to the size of the mean indicates the instrument is imprecise.
Range	Range refers to the span of concentrations the instrument can detect. The lower limit of the range is the minimum detectable concentration, a value that is not necessarily near zero. The upper limit of the range is a concentration value that does not exceed the instrument's upper calibration.
Reliability	Reliability is operation of the instrument without mechanical or electrical failure. An instrument requiring frequent repair will require frequent calibration checks and cannot be trusted. Reliability will be decreased with frequent repair.
Stability	Stability refers to the ability of an instrument to respond in the same way over a long period of time. Two performance parameters of stability are calibration and zero drift.
Response	Response time refers to the time lag between the point at which the sample enters the system and the point at which the instrument displays 90% of the sample concentration. Fast response time is required when the gas or vapor concentration fluctuates wildly, and/or when the concentration is governed by a ceiling limit concentration that should not be exceeded, even momentarily.

Table I-40
CRITERIA FOR INSTRUMENT EVALUATION (Continued)

Criteria	Description
Sensitivity	Sensitivity refers to the minimum amount of the gas or vapor being studied that will provide a repeatable signal which is distinguishable from the background noise. One specification of sensitivity is the "lower detectable limit," which is the minimum pollutant level that will provide a signal at twice the noise level.
Specificity	Specificity is the lack of instrument response to gases or vapors other than the one under study.
Zero drift	Zero drift refers to deviation from zero reading over time. The drift can be due to instability in sample flow rate, to temperature sensitivity of the instrument, and to degradation of the sensor (20).

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AIR SAMPLING FOR PARTICULATES

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Exposure to airborne contaminants in the work environment has been linked to a wide spectrum of occupational diseases. A serious problem has existed over the years in occupational health in that much of the medical and epidemiological research data collected on workers has not had companion occupational environmental data collected in the time interval over which exposures occurred. The evaluation of worker exposure to potentially hazardous agents in the workplace is essential to establishing cause/effect relationships between an occupationally related illness and a specific agent(s). Existing gaps in worker exposure data have greatly limited the establishment and promulgation of proper occupational health standards for our nation's work force.

The purpose of this chapter is to describe current procedures and methods employed by industrial hygienists to assess, measure, and characterize worker exposure to potentially hazardous contaminants in the occupational environment. The chapter is divided into two sections: sampling techniques for gases and vapors and techniques for particulate sampling.

INTRODUCTION

Particulates of concern relative to respiratory diseases are those suspended in air which can be inhaled. This includes all particles, solid or liquid, in a size range capable of being inhaled and deposited in the nasopharyngeal and/or tracheobronchial region, or penetrating the tracheobronchial tree and being deposited in the alveolar regions of the lung. An aerosol is any system of liquid or solid particles dispersed in a stable aerial suspension. An aerosol must be of fine enough particle size and consequent low settling velocity to possess considerable stability as an aerial suspension (34).

Particulate material can be classified, according to its physical state and evolutionary character, into liquid aerosols or solid particulates. Liquid aerosols are generally classified as fogs or mists. Liquid aerosols are normally formed by condensation from a gaseous to a liquid state (fog), or by dispersion of a liquid due to splashing or foaming, by atomization, and by gas entrainment of a liquid (mists). Solid particulates are further subdivided according to particle size and method of evolution into dusts, fumes, and smokes.

Dusts. Dusts are formed from solid organic or inorganic materials when the parent material (the material from which they are formed) is reduced in size through some mechanical process such as crushing, drilling, grinding, blasting, and pulverizing. Dusts vary in size from visible to submicroscopic, but the composition of individual particles is not changed because of the size reduction process *per se*. Airborne dusts range in size from < 0.1 to $25 \mu\text{m}$ in diameter.

Fumes. Fumes are extremely fine, solid particulates formed by processes such as combustion or condensation. The term is generally applied to the condensation of metals from their gaseous state after volatilization and the subsequent formation of metal oxides. Examples are metallic fumes formed from welding and thermal cutting operations. Fumes generally range in size from 0.001 to $1.0 \mu\text{m}$.

Smoke. Smoke refers to airborne particulates resulting from the incomplete combustion of organic materials. Smoke particles are usually less than $0.5 \mu\text{m}$ in diameter.

An aerosol's nature is an important factor in developing or selecting methods for characterization of the environment. Particulate sam-

pling is performed by drawing a measured volume of air through a collecting device for removal of the particles of interest, or as discussed in a later section, some direct reading instruments pass the aerosol through a sensing region without particle removal (30). The particulate concentration is arrived at by the weight or number of particles collected per unit volume of air sampled. Mass determinations are made by gravimetric or chemical analysis as appropriate. The number of particles per unit volume is determined by counting the number of particles in a known portion of the sample. Although in the past, particle counts have been used to assess health hazards from inhalation of insoluble particulates, the mass of the material entering the lung provides the best estimate of toxic effect (1).

The fraction of particles in inspired air which is retained in the respiratory tract and the site of deposition is dependent upon 1) the aerodynamic properties of the particle, i.e., the size, shape, and density; 2) the size and shape of the airways; and 3) the pattern of breathing, namely, nose versus mouth breathing (27). The aerodynamic size or diameter is equal to the diameter of a unit density, spherical particles having the same settling velocity as the particle in question. Unless otherwise specified, all sizes mentioned relate to the aerodynamic size or diameter of a given particle. The aerodynamic properties of a particle determine its mobility regardless of its apparent size and shape. Thus, a relatively large, loose aggregate of particles may behave aerodynamically the same as a much smaller dense particle.

The aerodynamic properties of particles determine the relative ease with which they are removed by the physical mechanisms of inertial impaction, sedimentation, and diffusion (6)(33). For particles with an aerodynamic size of 5 to 30 μm , inertial impaction is the primary mechanism responsible for deposition in the respiratory tract. The inertia of inhaled particles will tend to cause them to resist changes in direction and impact upon the airway walls where airflow is deflected by branching. Deposition by inertial impaction for a given aerodynamic particle size will increase with increases in air velocity; thus, this mechanism operates primarily in the nasal chamber and upper respiratory tract.

Sedimentation, or gravity settling, is the second mechanism responsible for particle deposition in the respiratory tract (6). When a particle

is released from rest and falls in air, it will accelerate to a terminal settling velocity where the downward force of gravity is balanced by the opposing aerodynamic drag of air through which the particle is falling. When respirable particles reach terminal settling velocity, they are removed as they are deposited on airway walls or alveolar surfaces. Deposition in the respiratory tract from sedimentation predominates for particles in the 0.5 to 5.0 μm range that are not effectively removed by impaction and deposition from sedimentation usually occurs in the tracheobronchial region.

The third mechanism promoting particle deposition in the lungs is diffusion or Brownian motion. All airborne particles are moving at random, owing to their constant bombardment by gas molecules in air. Particles smaller than 0.5 μm , and especially those less than 0.1 μm , have such a small volume and mass that they have significant Brownian motion; this tends to cause them to be deposited readily (30). Deposition by diffusion predominates in the alveolar region, but it also occurs in the tracheobronchial region.

The aerodynamic properties of a fiber present a special case with regard to site of deposition. A fiber can be characterized by its long length to width (or aspect) ratio (which in the case of asbestos has been defined at an aspect ratio of 3:1). As with other particles, the settling velocity of a fiber is largely dependent on its diameter (43). Fibers in a moving airstream tend to align their length parallel to the direction of air flow and behave much the same as a spherical particle of the same cross-sectional diameter. If the fiber shape is curved or curled, it will have an end-on aspect equal to the width of the curl or curvature and will have a much greater chance for deposition than straight fibers.

PULMONARY DEPOSITION

Experimental studies and models to predict the extent of particle deposition within the respiratory tract have been reported in various articles, reviews, and symposia by Brown, et al. (7), Landahl, et al. (20), Altshuler, et al. (3), Van Wijk and Patterson (37), Weibel (41), Davies (12)(13), Lippmann and Albert (25), Lippmann (23), Casarett (8), and others. Hatch and Gross (19) summarized characteristics of particle deposition at various depths within the respiratory system as follows:

1. Particles larger than 10 μm equivalent diameter are essentially all removed in the nasal chamber and therefore have little probability of penetrating to the lungs. Upper respiratory efficiency drops off as size decreases and becomes essentially zero at about 1 μm .
2. The efficiency of particle removal is high in the pulmonary airspaces, being essentially 100% down to around 2 μm . Below this size, it falls off to a minimum at about 0.5 μm . It increases again as the force of precipitation by diffusion increases with further reduction in size.
3. The percentage penetration of particles into the pulmonary airspaces rises from essentially zero at 10 μm to a maximum at and below about 1 μm where it equals the fraction of tidal air which reaches the lungs.
4. The percentage of inhaled particles which penetrate to and are deposited in the pulmonary airspaces has a maximum value between 1 and 2 μm . Larger particles are deposited in the lungs in lesser degree because they are trapped higher up in the respiratory tract. Lung deposition of finer particles falls off because the local efficiency of removal decreases as size diminishes below 2 μm .
5. Below 0.5 μm , the probability of deposition in the pulmonary airspaces rises in proportion to the increase in the force or precipitation by diffusion with decreasing size.
6. The relative amount deposited and the distribution of the collected particles in the respiratory system changes with breathing frequency and tidal volume. Upper respiratory trapping increases as the rate of inspired airflow goes up with faster breathing frequency. The magnitude of deep-lung deposition increases with slow, deep breathing because of the larger fraction of tidal air which reaches the pulmonary spaces and the longer transit time of air into and out of the lungs.

STANDARDS AND CRITERIA FOR RESPIRABLE DUST SAMPLES

Two types of samples referred to as "respirable" and "total" gained considerable im-

portance with the promulgation of occupational exposure standards requiring mass particulate sampling. Prior to the adoption of mass particulate sampling, insoluble pneumoconiosis dusts were evaluated using the impinger method. With impinger sampling, air is drawn through a liquid (usually water or alcohol) at a known flow rate over a measured period of time. After collection of the dust particles in the impinger solution, the dust particles in a portion of the sample solution are counted microscopically and used to calculate the airborne dust concentration expressed in millions of particles per cubic foot (mppcf) of air. Although this method is useful in determining the dust concentration to which workers are exposed, it is tedious, imprecise, and more importantly, a mass determination is a better indicator of health risk. Likewise, since total mass concentrations may be determined principally by larger particles which cannot penetrate the upper respiratory tract and thus cannot damage the deep lung tissue, total dust has been judged not to be a reliable measure of hazard from exposure to the insoluble pneumoconiosis-producing dusts.

Three different criteria have been specified for "respirable" dust measurement: that of the British Medical Research Council (BMRC), which was later adopted by the Johannesburg International Conference on pneumoconiosis in 1959; that of the U.S. Atomic Energy Commission's Office of Health and Safety, adopted at a 1961 Los Alamos conference; and that adopted in 1968 by the American Conference of Governmental Industrial Hygienists.

As stated in the recommendations of the Johannesburg Conference (28) the BMRC criterion is:

measurements of dust in pneumoconiosis studies should relate to the 'respirable fraction' of the dust cloud, this fraction being defined by a sampling efficiency curve which depends on the falling velocity of the particles and which passes through the following points: effectively 100% efficiency at 1 micrometer and below, 50% at 5 micrometers, and zero efficiency for particles of 7 micrometers and upwards; all the sizes refer to equivalent diameters. (The equivalent diameter of a particle is the diameter of a spherical particle of unit density having the same falling velocity in air as the particle in question.)

According to Davies, a size selective sampling device meeting the criteria would generate a curve of sampling efficiency versus aerodynamic size as illustrated in Figure I-9 and is defined by the percentage removed by the selective sampler as follows (11):

% Rejection	Diameter (μm)
10%	2.2
20	3.2
30	3.9
40	4.5
50	5.0
60	5.5
70	5.9
80	6.3
90	6.9
100	7.1

*For spheres of unit density

The BMRC criterion for a size selective sampler is met by a horizontal elutriator device consisting of stacked parallel plates (18)(39). Although the rejection curve is theoretical, it can be approximated by carefully built commercial devices.

The Atomic Energy Commission Standard defined "respirable dust" as that portion of inhaled dust which penetrates to the nonciliated portions of the lung (19). This criterion for respirable dust sampling was developed for evaluation of insoluble internal radiation emitters and was not intended for particles which are readily soluble in body fluids and those which are chemical intoxicants (23). The criterion adopted defined "respirable dust" as follows:

Size* (μm)	Respirable (%)
10	0
5	25
3.5	50
2.5	75
2	100

*Sizes referred to are equivalent to an aerodynamic diameter having the properties of a unit density sphere.

The Los Alamos curve is illustrated along with the BMRC curve in Figure I-9. The Los Alamos curve was not developed with any particular size selective sampler in mind; however, it is approximated by several cyclone inertial collectors (39). Mathematically it has been shown that the mass collected on the second stage of

an instrument meeting the AEC criterion will be slightly less than that passing an instrument meeting the BMRC criterion (4)(40).

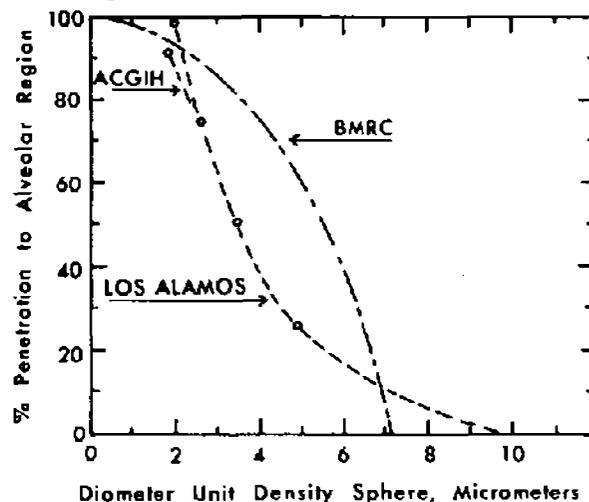


Figure I-9. "Respirable" dust mass measurement sampling criteria (1).

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In 1968, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted a quartz TLV for respirable dust in milligrams per cubic meter (mg/m^3) (1). This allowed an alternate mass concentration method for evaluation of quartz, cristobalite, and tridymite (three forms of crystalline-free silica) to supplement the method based on particle count concentrations. The alternate concentration TLV proposed was:

$$(1) \text{ for respirable dust in } \text{mg}/\text{m}^3$$

$$\frac{10 \text{ mg}/\text{m}^3}{\% \text{ Respirable Quartz} + 2}$$

NOTE: Both concentration and % Quartz for the application of this limit are to be determined from the fraction passing a size-selector with the following characteristics:

Aerodynamic Diameter (μ)	≤ 2.0	2.5	3.5	5.0	10
% passing selector	90	75	50	25	0

(2) for "total dust" respirable and non-respirable:

$$\frac{30 \text{ mg}/\text{m}^3}{\% \text{ Quartz} + 2}$$

NOTE: For both cristobalite and tridymite: Use one-half the value calculated from the count or mass formulae for quartz.

It can be seen in Figure I-9 and from the specification that the size selective characteristics of the ACGIH and the AEC criteria differ only at 2 μm : the ACGIH allows for 90% passing the size-selector versus 100% for the AEC criterion.

The ACGIH recommendation was not designed to fit a particular sampling instrument. However, the small cyclone closely approximates these criteria and is commonly used for this purpose. Standards promulgated under the Occupational Safety and Health Act of 1970, the Coal Mine Health and Safety Act of 1969, and the Federal Mine Safety and Health Act of 1977, require "respirable" dust sampling for evaluation of pneumoconiosis-producing dusts. For certain toxic dusts that are highly soluble in body fluids, the absorbed dose is most important and "total" dust samples are more appropriate.

METHODS OF COLLECTION

A particulate sampling train consists of the following components (30): air inlet, particulate separator or collecting device, air flowmeter, flowrate control valve, and air mover or pump. Of these, the most important component is the particulate separator. The sampling efficiency and reliability of the separator must be high. The pressure drop across the collector should be low in order to keep to a minimum the size of the required vacuum source, motor, and power supply. The separator may consist of a single element (such as a filter or impinger), or there may be two or more elements in a series (such as a two-stage cyclone or multi-stage impactor) so as to characterize the particulate into different size ranges.

There are a variety of techniques that have been used or suggested for collecting airborne particulates. This review will discuss techniques used in the collection of airborne particulates rather than specific instruments. The techniques have been grouped into seven general categories based on the physical forces employed for collection. Overlap exists among some categories. Table I-41 presents a summary of the techniques with operating principles and examples.

Filters

The use of filters has become the most common method of collecting airborne particulates. Advantages include low cost, simplicity, small space requirement for storage, and a wide choice of available filter media and sizes.

Several mechanisms are involved in filtra-

tion. These include direct interception, inertial impaction diffusion, electrical attraction, and gravitational forces. One or more of these mechanisms will predominate in a given case and will depend on the flow rate, the nature of the filter, and the nature of the aerosol (22). For example, with fibrous filters and membrane filters, particles are removed from the gas stream primarily by impaction and diffusion mechanisms. The principles of direct interception and electrostatic deposition may also be present but, in the case of fiber and membrane filters, usually are less important. Retention of particles by impaction and diffusion mechanisms is largely dependent upon particle size.

Since a variety of mechanisms are involved in filtration, the collection efficiency of a given filter for a given particle size should vary with face velocity and particle size (22). A typical efficiency curve for a given filter and aerosol may be high at low velocities (primarily due to diffusion). With increasing face velocity, the efficiency would first fall off and then, with higher velocities, begin to rise as a result of inertial collection effects. At very high velocities, forces exerted on the particle by the flowing gas stream may be greater than the forces of adhesion and re-entrainment of the collected particle may occur. A similar efficiency curve will result from a given filter and a given face velocity; i.e., for small particles, a high collection efficiency exists; as particle size increases, the efficiency of the filter at first drops off and then increases for larger size particles. Several types of filter materials are virtually 100% efficient for essentially all particle sizes. Information regarding the specifications and performance characteristics of most types of commercially available filter material is presented in tabular form in "Air Sampling Instruments for Evaluation of Atmospheric Contaminants" (22).

Fibrous filter media used for sampling particulates are available in a wide variety of matrices including cellulose fiber, glass fiber, mixed fiber, and plastic fiber (22). Fibrous type filter media consist of fine, thickly matted fibers and have a low mass per unit face area, making them ideal for gravimetric analyses. Cellulose fiber filters have been used primarily for liquid-solid separations by analytical chemists. They are relatively inexpensive, have a wide range of sizes, excellent tensile strength, and a relatively low ash content. Their major disadvantage is their

Table I-41

SAMPLING TECHNIQUES FOR COLLECTION OF AIRBORNE PARTICULATES

Sampling Technique	Force or Mechanism	Examples
Filters	Combination of inertial impaction, interception, diffusion, electrostatic attraction, and gravitational forces	Various types and sizes of fibrous, membrane, and nuclear pore filters with holders
Impactors	Inertial—Impaction on a solid surface	Single and multi-jet cascade impactors and single-stage impactors
Impingers	Inertial—Impingement and capture in liquid media	Greenburg-Smith and midget impingers
Elutriators	Gravitational separation	Horizontal and vertical type elutriators
Electrostatic Precipitation	Electrical charging with collection on an electrode of opposite polarity	Tube type, point-to-plane, and plate precipitators
Thermal Precipitation	Thermophoresis—particle movement under the influence of a temperature gradient in the direction of decreasing temperature	Various devices have been designed for particulate collection for microscopy analysis
Cyclones	Inertial—Centrifugal separation with collection on a secondary stage	Tangential and axial inlet cyclones in varying sizes.

hygroscopicity, which makes accurate gravimetric analyses difficult. Glass fiber filters have low airflow resistance, reduced hygroscopicity, and minimal interference with analytical chemistry methods making them well suited for gravimetric, chemical, and physical analysis. Silica and some trace metals will interfere and this needs to be considered when selecting glass fiber filter media.

Membrane filters produced by precipitation of a resin under controlled conditions, and nuclepore filters, produced by bombarding polycarbonate sheets with U-235 fission fragments and subsequent controlled etching, are widely used for collecting mineral dust for examination by optical and electron microscopy. Membrane filters are also ideal for gravimetric, chemical, and physical analysis because of their characteristics of very low mass, minimal hygroscopicity, and negligible ash content; and some are completely soluble in organic solvents. Membrane and nuclepore filters differ from fibrous filters in that particle collection takes place at or near the surface of the filter. This is an advantage for

microscopic examination but a disadvantage in that as the membrane loads up with particulate, the pressure drop increases and the deposit tends to slough off the filter.

Impactors

Inertial impactors operate on the principle that if particles in a moving airstream are suddenly deflected from a straight course, the momentum of the entrained particles may cause them to deviate from the streamlines of airflow and impact against the deflection surface (29). The particles are said to be "impacted" and the deflecting obstacle is operating as an impaction surface.

Impactors have been in use for many years and are particularly useful for determining the particle distribution of an aerosol. They are constructed as single-stage impactors with very narrow ranges of particulate capture or as a series of jets and impactor plates which provide particle separation into several size ranges. Impactor design may use a single jet or multi-jet nozzle

arrangement. The multi-jet variety is often preferred because particle bounce and blow-off are minimized and collection of larger samples is possible (15). Particles adhering to each stage or plate can then be weighed, counted, or analyzed. When an impactor has been properly calibrated for a given aerosol, it is possible to determine the aerodynamic median size characteristic of each stage. A particle analysis may be made by calculating the percent-by-weight on each stage using weighings, radioactivity, or quantitative analysis.

Multiple stage impactors utilize an extension of the theoretical finding that increasing jet velocity, coupled with decreasing jet cross section, results in a predictable size separation.

Impaction devices employ a wide variety of materials for particle collection surfaces: filter paper, glass, stainless steel, nutrient agar, mylar, and teflon. Some collection surfaces are coated with a nondrying adhesive film to insure adequate retention of impacted particles. In most instruments, a high efficiency filter is used as a back-up to collect submicrometer particles smaller than the cut-off size of the last stage.

Impingers

The impinger is one of the oldest devices for measurement of particulate. Greenburg and Smith developed the original version of the impinger in 1922 (17). Littlefield and Schrenk introduced a midget version of the standard impinger in 1928 (26). Use of the impinger for particulate sampling has diminished in recent years; it is usually only selected for situations where the dust count or number of particles expressed in "millions of particles per cubic feet of air (mppcf)" is desired.

The impinger consists of a calibrated glass flask and glass nozzle or jet submerged in a liquid (usually water or alcohol). Air is drawn through the nozzle at a high velocity, the particles impinge on a flat plate or on the glass bottom of the tube, lose their velocity, are wetted, and become trapped by the liquid. A small sample of the liquid is then counted in a special cell using light microscopic techniques. Particles may also be sized in a similar manner.

Particles of 1.0 μm in diameter and greater are efficiently collected by the impinger. The efficiency rapidly drops off for particles smaller than 0.7 μm (14). To obtain the maximum efficiency for small particles, the jet must be oper-

ated as a critical orifice so that the particles impinge at or near sonic velocity (29). Such velocities can lead to problems of shattering of coarse particles and aggregates and may give erroneous results (31).

Elutriators

Elutriators have been widely used in two-stage sampling trains, as preselectors at the front of the sampling train, for removal of coarse particulate matter, and for collection of the smaller size fraction on a filter or other suitable device. Elutriators are classified as horizontal or vertical, based upon their design and orientation in operation.

Horizontal elutriators were first recommended for use as a two-stage respirable-dust sampler in 1952 (42). When considering a standard for pneumoconiosis-producing dusts the British Medical Research Council (BMRC) selected the horizontal elutriator as the most appropriate dust sampling instrument for matching experimental lung deposition data. The council defined respirable dust as that passing an ideal horizontal elutriator.

A vertical elutriator developed by Lumsden and Lynch was recommended by NIOSH as the instrument of choice for determining worker exposure to cotton dust (10).

Elutriators function much like inertial separators, except that they operate at normal gravitational conditions whereas inertial separators induce multi g forces by angular acceleration to achieve separation of particles (39). A falling particle will accelerate until it reaches equilibrium with the resistance forces acting against it. This falling speed is defined as the particles' "terminal velocity" and will vary according to the particle diameter and density and the viscosity and density of the airstream. Terminal velocity also varies in a predictable manner dependent upon whether the airflow is streamline, intermediate, or turbulent (14). In practice, particles of specific sizes are removed from an airstream by gravity while smaller particles remain suspended and are collected for subsequent analysis.

The horizontal elutriator contains a series of thin rectangular ducts, one above the other, connected in parallel to a common exit (39). Dust-laden air flows at a constant rate across the plates where large particles settle out. Smaller particles are carried through the preselector and

are collected on a filter which is either weighed or chemically analyzed.

Vertical elutriation uses the same principle of gravitational force to separate the particles into fractions, but differs in that with vertical elutriation, the gravitational force works in a direction opposite to induced airflow instead of normal to it (32). The vertical elutriator is a vertical tube with parallel sides designed such that particles above a certain design cut-off size will not penetrate the tube. Smaller particles pass through the elutriator stage and are collected on a filter. A variety of filter materials have been used for both vertical and horizontal elutriators.

With elutriators, various sampling efficiencies versus particle size can be accomplished by varying flow rates and sampler dimensions. For both vertical and horizontal elutriators, it is difficult to achieve perfect streamline flow. Also, flow rate is extremely critical: if too high, a disproportionate percentage of larger particles are collected on the filter; if too low, more large particles are removed causing errors on the low side. Elutriators must be operated in a stationary position and thus personal or breathing zone samples are not practicable.

Electrostatic Precipitation

Electrostatic precipitators have been used for many years for particulate sampling and are a modification of the Cottrell Precipitator (9). Electrostatic precipitators operate by imparting one or more electrical charges to particles which are then attracted to a collection electrode of opposite polarity. Although particles may acquire electrical charges by several means, e.g., friction with solid matter, ionization in flames, absorption of energy from ionizing radiation, etc., the high voltage corona discharge is usually employed for electrostatic precipitators. The attraction of the charged particles to the collecting surface is a function of the number of charges acquired, the field gradient, and the viscous drag of air (21).

Electrostatic precipitation differs from other methods discussed in that the electrical forces acting to separate suspended particles from the airstream exert their force directly on the particle and not on the entire gas volume. Therefore, the method requires relatively little power to precipitate the particles or to move the gas stream through the collector. In contrast, mechanical collectors such as cyclones, impac-

tors, impingers, and scrubbers consume most of the power (associated with collection) to move the gas through the collector, and the high collector efficiency is associated with a large pressure drop (21). Advantages of electrostatic precipitators include negligible flow resistance, no clogging of the collector, and precipitation on a metal electrode whose weight is unaffected by humidity.

Electrostatic precipitators have three general electrode configurations: (1) concentric, (2) parallel, and (3) point to plane. The most common configuration used in particulate sampling is the concentric or wire and tube system (3). The tube is usually a light alloy cylinder about 6 inches long and 1½ inches in diameter, positioned horizontally and grounded. The cylinder can be lined with filter media if precipitation on a filter is desired. A stiff wire aligned along the center of the tube and supported at one end serves as the charging electrode. A high DC voltage is applied to the electrode and the corona discharge from the wire tip charges particles in the airstream drawn through the tube. The electrical potential gradient between the charging electrode and the collecting tube causes the particles to be attracted to the inside surface of the tube.

Thermal Precipitation

In thermal precipitation, the airstream is passed through a narrow space which has a significant temperature gradient perpendicular to the direction of flow. The movement of a particle in the direction of decreasing temperature (called thermophoretic velocity) causes the particle to be deposited on a relatively cool collecting surface (36). In a sampling instrument, the air is drawn past a heated wire or plate and the dust collects on a cold glass or metal surface opposite the hot element. A high thermal gradient is needed so the channel between the wire or plate and the collecting surface is kept small. Because the migration velocity induced by the thermal gradient is small, the system is limited to low volumetric flowrates and thus is used only for collecting sufficient particulates for microscopic examination.

Cyclones

Cyclones have found increasing use in recent years as the first stage in two-stage samplers for respirable mass dust exposure determina-

tions. The sampling unit, usually a 10 mm cyclone and filter holder assembly, is attached to a low-flow pump and worn by the worker such that personal samples are obtained. Cyclones are also available for fixed location, high-volume sampling.

General principles of centrifugal and gravitational forces are used in the cyclone sampler to separate aerosols into various size fractions. Air is drawn through the cyclone at a preselected flow rate. The sample enters the cyclone tangentially and as the centrifugal motion of the flow increases, the inertia of the larger, non-respirable particles forces them to concentrate at the flow periphery where they are separated and collected in a removable section at the bottom of the cyclone. The smaller, respirable particles remain in the cyclone's airstream and are collected on a preweighed filter.

Cyclones are constructed with a variety of materials; the most common are nylon or stainless steel. Plastic cyclones are unacceptable because an electric charge may accumulate on the plastic and alter the collection characteristics (5). The respirable fraction of the dust sample is collected on a variety of high-efficiency filter materials. The nonrespirable portion can also be recovered and weighed, providing "total" dust exposure as well.

There is considerable disagreement about the collection efficiency characteristics of these instruments. Since their efficiency is flowrate dependent, operation at nonstandard flows will cause errors in both total and respirable values (24).

By design, cyclones used for respirable dust sampling are highly efficient for removal of larger particles (i.e., greater than 10 μm) and are not efficient for particles below about 2 μm .

Direct Reading Instruments

The aerosol sampling methods discussed thus far differ from direct reading methods in that the aerosol is removed from the airstream for subsequent analysis, e.g., gravimetric analysis, chemical analysis, or optical or electron microscopy. Direct reading methods are more complex: the sampling and analysis is performed within the instrument and the property of interest is displayed continuously or after a brief sampling period.

Direct reading methods are similar in that the aerosol is either passed through or collects

upon a sensing region (35). The presence of the aerosol is detected by a change in some property of the system caused by the particle or particles within the sensing region. The instrument is designed to make use of some relationship between the detected change and some property of the aerosol.

There are a variety of direct reading instruments on the market for analyzing airborne particulates according to particle size, aerosol number, and aerosol mass concentration. The sensitivity of these instruments is limited by the random property fluctuations of the accompanying gas molecules and by the noise level of the electronic circuitry which converts the detected change to an electronic signal (35). The accuracy of the method is dependent upon the relationship of the change detected in the sensing zone and the aerosol property measured. This relationship is determined mathematically from the operating principle of the method and verified by an empirical relationship using a well-characterized aerosol system. Because of the wide variation in size, shape, aerodynamic properties, and refractive indices of industrial aerosols, there may be an unknown relationship between the sensing zone change detected and the aerosol property measured so that an inaccurate particle measurement is indicated. Likewise, the user of direct reading instruments must be careful in comparing measurements from instruments having different operating principles, as such comparison is likely to give contradictory information.

Optical Direct Reading Instruments—A significant number of particulate direct reading instruments operate on the principle of the interaction between the particles and visible light (35). These instruments may be categorized according to whether the sensing zone contains one or numerous particles at a given time. Multiparticle instruments include transmissometers, nephelometers, and photometers.

Transmissometers operate on the basis of the extinction of light by particles. These instruments are somewhat limited: in order to get a measurable change in light extinction, the sensing volume must contain a large number of particles. This means there must be either a high concentration of particles or a long path length. Transmissometers are used to monitor particulate stack emissions because of the high particle concentration within the stack.

In integrating nephelometers, the small volume (about 1 L) of illuminated particles and the light scattered at a particular range of angles by the particles is measured by the photoreceptor (38). The instrument is simple in construction and has been adapted for use in studies of urban and rural atmospheric aerosol pollution to measure particles primarily in the 0.1 to 1.0 μm range. Similar to nephelometers, forward scattering photometers are available which employ an incandescent light source and optics similar to dark field microscopy (35). A narrow cone of light converges on an aerosol but is permitted to scatter only in the near forward direction, striking the photocell receptor. The signal from the photocell is converted to mass or number of particles per unit flow rate.

Single particle light scattering instruments all employ a small sensing volume and a light source either from an incandescent lamp or a laser source. In all single particle instruments, it is important to avoid coincidence errors resulting from more than one particle being in the sensing zone simultaneously. The manufacturer usually specifies the maximum number that can be handled without producing coincidence errors.

Electrical Direct Reading Instruments—The acquisition of an electrical charge by a particle is the basis for four types of electrical direct reading instruments: mobility analyzer, contact electrification probe, ion interception chamber, and flame ionization detector. Unipolar ions, radioisotopes, and hydrogen flame have been used to impart a charge to the particles, the amount being generally dependent upon particle size.

Beta Attenuation Direct Reading—Instruments have been designed and are commercially available which detect the mass concentration of an aerosol cloud. Detection is based on the attenuation of beta radiation resulting from collection of a sample of dust between comparative readings of a beta radiation source (32). The instrument uses a cyclone precollector to separate the respirable from the nonrespirable fraction. The respirable particles pass to the second stage through an orifice and are impacted on a polyester impaction disk. The impaction disk is placed between a beta radiation source and a detector. Particles deposited by impaction on the plastic film increasingly absorb the beta radiation reaching a Geiger-Muller detector from a Carbon-14

source. This beta-attenuation principle is advantageous because the penetration of low energy beta radiation depends almost exclusively on the mass-per-unit area of the absorbing substance and on the maximum beta energy of the impinging electrons; however, it is independent of the chemical composition or physical characteristics of the absorbing substances.

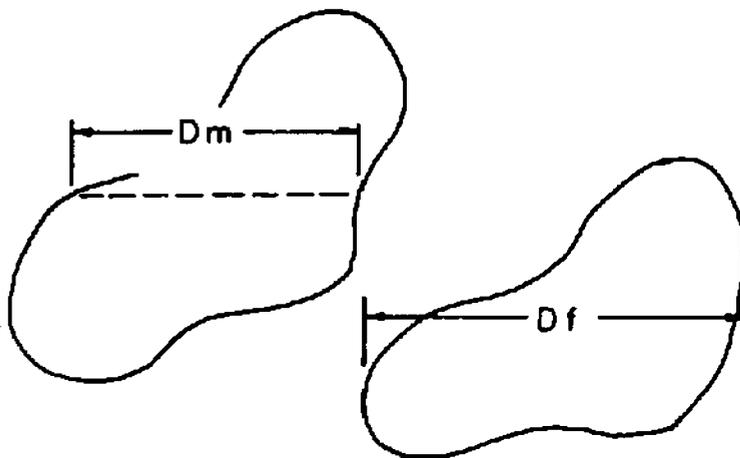
Piezoelectric Direct Reading Instruments—An instrument for direct measurement of particulate mass concentration is the piezoelectric crystal mass monitor (35). In the original design of the instrument, particles drawn through an impactor inlet to separate the respirable from nonrespirable fraction, are charged using electrostatic precipitation, and are deposited on the face of a quartz crystal. The crystal is part of an oscillator circuit whose resonant frequency is a linear function of the crystal mass. As particulate mass collects on the crystal face, the frequency changes to reflect the added mass. The rate of frequency change of the crystal is related to airborne mass concentration. Some piezoelectric instruments use a parallel crystal (which is not subjected to particle loading) as a reference standard to correct for temperature, pressure, or humidity changes in the air.

PARTICULATE SIZING

The ability of a particle to reach the deep lung tissue and cause an adverse effect is dependent, in part, upon its size. The characterization of an aerosol by particle size, therefore, is important in understanding the mechanisms of respiratory disease. Sizes generally thought to be "respirable" fall into the range below 10 μm .

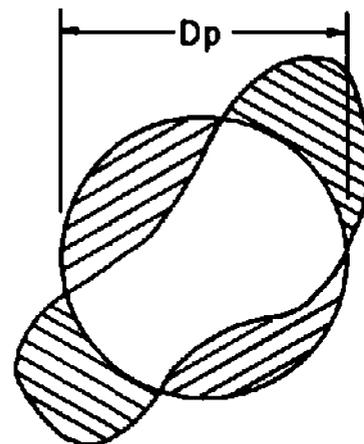
The problem of size determination is complicated by the enormous range of sizes encountered in the workplace, e.g., from 0.001 μm for certain metallic fumes to 100 μm for a variety of industrial dusts. Other factors, such as particle density and shape, are also influential in determining the behavior of an aerosol. Any sample of airborne dust may contain a wide range of particle shapes and densities.

Since most dusts encountered in the workplace are irregular in shape, several methods have been developed to determine which dimensions to use for particle diameter. "Martin's diameter" is the length of a line which divides the two dimensional projection of a particle into two equal areas. The line for the initial particle



MARTIN'S DIAMETER

FERET'S DIAMETER



PROJECTED AREA DIAMETER

Figure I-10. Geometric diameters for irregularly shaped particles.

measured may be drawn in any direction, but lines for all other particles measured on that observed field must then be drawn parallel to the first (See Figure I-10). "Feret's diameter" is the distance between the extreme boundaries of the particle image. As with Martin's diameter, all measurements should be made in the same direction. The "projected area diameter" is the diameter of a circle having the same cross-sectional area as the particle image (16). Using only the average (mean or median) diameter is not sufficient to adequately describe the aerosol in question. Information about how the particle sizes are distributed about the mean (the standard deviation) is also important. If the particle sizes in an aerosol are normally distributed, i.e., in a bell-shaped fashion as depicted in Figure I-11, then approximately 67% of all particle diameters fall within one standard deviation of the mean, 95% within two standard deviations, and 99.7% within three standard deviations.

However, it has been found that most industrial dusts have particle size distributions skewed toward the smaller size (Figure I-12). Hatch and Gross pointed out that a log-normal distribution more closely approximates size frequency of airborne dusts than does a normal distribution (19). If particle size distribution data are plotted with the logarithm of particle size, the skewed curve is transformed into a sym-

metrical or bell-shaped curve (Figure I-13). If the assumption of a log-normal distribution is correct, then a cumulative frequency plot of the particle size data on log probability coordinates will be a straight line as shown in Figure I-14. We can then read the geometric mean particle size or 50% size (median size) directly from the graph. Particle size distribution can also be determined graphically by dividing the 84.13% size by the 50% size, or by dividing the 50% size by the 15.87% size. The value obtained is the geometric standard deviation, which, along with the geometric mean particle size, is a satisfactory description of the particle size distribution.

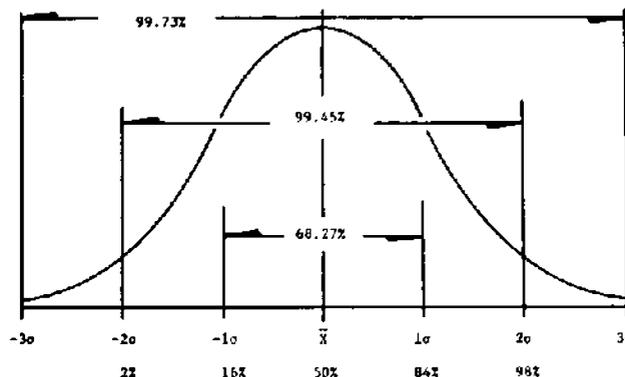


Figure I-11. Normal or bell-shaped distribution. Generally, particle size distributions are not normally distributed.

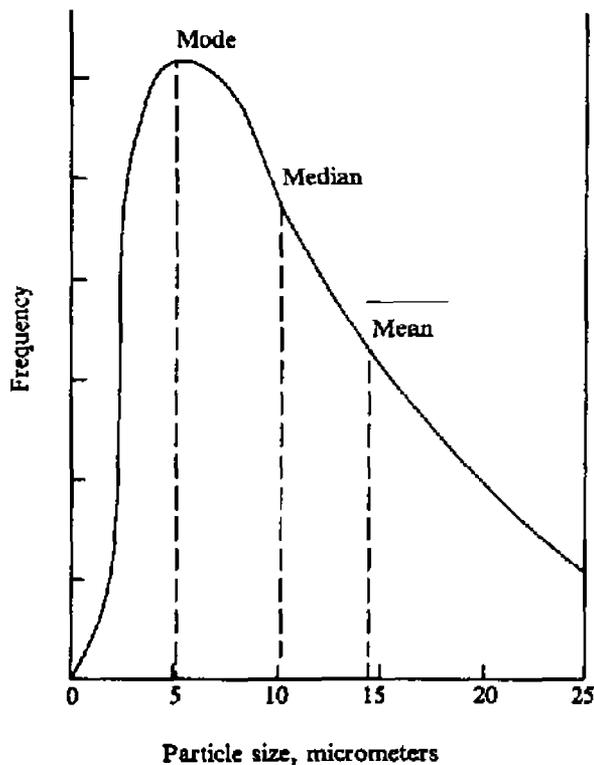


Figure 1-12. Skewed particles size distribution of a typical dust.

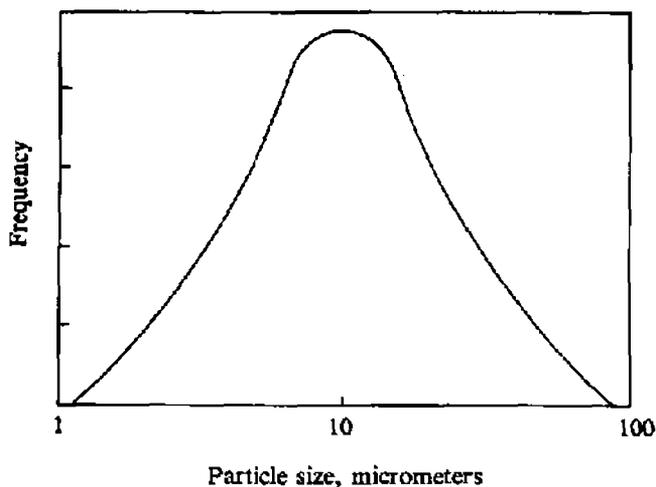


Figure 1-13. Particle size distribution of Figure 1-12. Plotted with the particle size on the log scale.

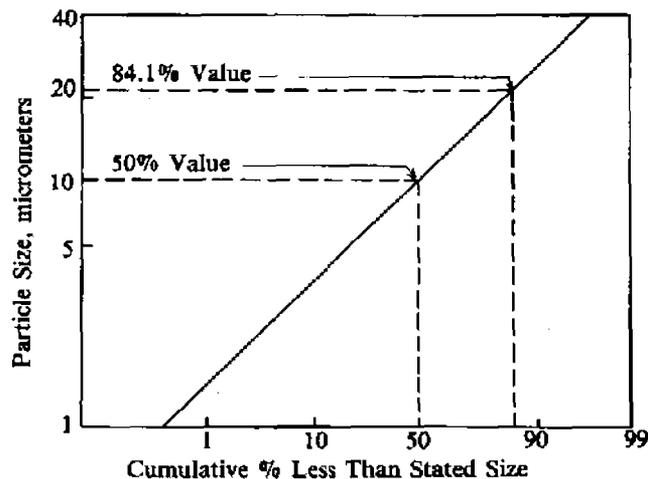


Figure 1-14. Cumulative log-probability plot for the particle size distribution of Figure 1-12.

Although the optical microscope has been the standard instrument for particle size analysis, there are a variety of other techniques commonly used for this purpose, some of which are described in previous sections (e.g., impactors, elutriators, cyclones, and direct reading devices). The selection of appropriate sampling and analytical instruments will depend on a number of factors related to the purpose of the sampling to be done, the character of the aerosol, the accuracy and precision required, etc. The electron microscope, for example, may find application in size determinations for industrial aerosols that are below the limits of resolution of the light microscope. However, the costs may be prohibitive in cases of limited application.

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SAMPLING MICROBIAL AEROSOLS

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INTRODUCTION

Collecting microbial aerosols is not substantially different from collecting any other airborne particulates. After collection, however, the processing of the sample is all important. These particles have life and the capacity to grow, multiply, and—as parasites—cause undesirable effects in a multiplicity of hosts. No chemical or physical measurement(s) available today can assess all these characteristics. Even detection of their presence often requires the bio-amplification provided by their growth characteristics. Many toxic materials are effective in the ppm ($1/10^6$) or even ppb ($1/10^9$) ranges; microbes may be active in the $1/10^{12}$ to $1/10^{14}$ concentrations. (For example, inhalation of a single tubercle bacillus (10^{-12} to 10^{13} gm) can initiate an active tuberculosis lesion.)

Both indoor and outdoor air are seas of microbial particles. Depending on local conditions, concentrations of viable particles will range from a few per ft³ to many thousands or even millions. Particles are nearly indistinguishable so that detecting a specific viable and infective type is a little like selecting a specific raindrop in a rainstorm. Only by careful choice of growth and assay procedures, can the microbes of interest be selected out of the collectate.

Some description of the important sources, receptors, and transport mechanisms in the transfer of infectious agents is useful in understanding how infections occur. People, the major subjects of our concern, can be targets, carriers, sources, or vectors. As such, they range from the "Typhoid Mary" carrier, or the person with a cold shedding virus, to the dairy worker whose boots are laden with foot and mouth virus which he spreads through a susceptible animal population. The sources of aerosolized material can include growth sites such as sewage treatment plants, infected surgical wounds, animals, soil,

people, and "other warm, moist and nutritive locations"(3). Microbial aerosols can also be dispersed directly from animate carriers or by activities disturbing an infected but normally passive source. For example, many respiratory infections of construction workers have been caused by soil fungi aerosolized at excavation sites.

Table 1-42 lists various occupations and some of the diseases workers may acquire through exposure to microbial aerosols. The route of infection may be oral, or through the respiratory system, conjunctiva, or open wounds, etc. Disease descriptions are general and limited to those resulting from infection with viable organisms. Exposure to nonviable organisms can also cause disease (primarily allergies or hypersensitization phenomena). The indication of routes of infection by "contact" includes all other routes. The frequent occurrence of alternate routes is at least one indication as to why it is difficult to establish a direct cause and effect relationship between microbial aerosols and infection.

By and large, with the exception of fungal infections, the airborne route of infection is not the predominant mode. Occupational diseases due to aerogenic exposure to microorganisms or their toxic products may not be the most frequent hazards in work areas, but they are so widespread and the severity so great that they must be given close attention. A variety of occupations provide opportunity for aerogenic exposure. In the case of anthrax infections of goat hair pickers and sorters, most infections were through skin breaks, but an estimated 3% were by the respiratory route (1).

Special emphasis is placed on sampling viral aerosols because sampling for these agents is difficult. The problem is not only the mechanics

Table I-42

Occupation	Infection	Agents	Possible Contact Infections?
Hospital workers (and patients)	Conjunctivitis, otitis, sinusitis, diarrhea, etc.	Staphylococcus sp., E coli	Yes
		Proteus sp., pseudomonads, viruses	Yes
			Yes
	Urinary tract infection	E. coli, Klebsiella sp. (bacteria)	Yes
	Surgical wound infection	Staphylococcus, aureus	Yes
	Skin infection	Staphylococcus, aureus	Yes
		Pseudomonads	Yes
Respiratory infections		Staphylococcus albus	Yes
		M. tuberculosis bacteria	Some
		Influenza virus	Few
Hepatitis		Rhino virus, Adeno virus	Yes
		Hepatitis virus	?
Microbiology laboratory workers (clinical and research)	Every infectious disease worked on including animal diseases	Bacteria	Yes
		Virus	Yes
		Rickettsiae	Yes
		Chlamydia	Yes
Stock handler	Glanders Brucellosis Tularemia (rabbit fever) Encephalitis	A. mallei (bacteria)	Yes
		Brucella sp. (bacteria)	Yes
		Francisella tularensis (bacteria)	Yes
		Equine encephalitis virus	Yes
Hair and hides handler	Anthrax Tetanus	Anthrax spores	Yes
		Clostridium, Tetanii (spores)	Yes
Rendering plant worker	Q-fever	Cox. Burnetii	Yes
Lab animal care	Almost all agents studied	Bacteria, virus, fungi	Yes
Pet shops operator	Psittacosis		Yes
Meat packing plant workers	Brucellosis	Brucella sp. (bacteria)	Yes
Poultry packers	Ornithosis, psittacosis	Various psittacine chlamydia	Yes
Construction site prep. workers, ventilation system repair men	Histoplasmosis Blastomycosis Aspergillosis	Histoplasma capsulatum (fungi)	No
		Cryptococcus (fungi)	No
		A. fumigatus	No

Table I-42 (Continued)

Occupation	Infection	Agents	Possible Contact Infections?
Farmers	Farmers' lung	Microspora faeni (fungi)	No
	Ornithosis	Various psitticine, chlamydia	Yes
	Coccidioidomycosis	Coccidioides immitis (fungi)	No
	Brucellosis	Brucella sp.	Yes
	Erysipelas	Fungi	Yes
	Newcastle disease	Newcastle virus	Yes
	Rocky Mountain spotted fever	Rickettsia	?
	Q-fever	C. burnetii	?
	Anthrax	B. anthracis spores	Yes
	Plague (bubonic and pneumonic)	Yersinia pestis (bacteria)	?

of particle collection; the most difficult part of the operation is handling the catch. Viruses are the smallest entities said to be "living" and require sites within our living cells to propagate. Most viruses are fastidious and require specific host cells in which to multiply. The process of multiplication is necessary if they are to be detected from the "sea" of other particulates always present.

Detection (sampling and assay) of viral aerosols is perhaps the most difficult aspect of sampling microbial aerosols. However, many of the problems in sampling for viruses are common to sampling other microbes and a listing of needed improvements is applicable to most microbial sampling work. Research on sampling is needed in the following general areas:

1. Development of samplers that will concentrate the aerosol, provide some particle size discrimination ranging from 0.1 to 50 μm , will work with minimal energy input and noise output, and will utilize a variety of collection media.
2. Development of collection media broadly useful in the collection of bacteria, fungi, rickettsia, and viruses with minimal loss of viability. The need is for material that will retain its physical characteristics for prolonged sampling periods and will, with some adjustment, provide the needed nutrients or stabilizers for optimal survival and recovery of viable particles.

3. Development of assay (and collection in some cases) and growth media or additives for a basic substrate that will facilitate the selection of the agents of interest. Currently available formulations do this to some extent but usually provide less than optimal growth conditions for the agent to be selected.

The very nature of these requirements points out that although we have some hardware and technology as described in the section following, we are not yet able to sample the air of a workplace and define hazardous conditions except in a few exceptional circumstances. There are deficiencies in instrumentation and sample processing procedures. Worse, there are no standards for allowable or tolerable burdens of airborne microbes. The presence of low concentrations of measles virus in the air of classrooms was detected by W. F. Wells in 1942 (11). The presence of tubercle bacilli in a tuberculosis ward was demonstrated by R. L. Riley in 1961 by the use of sentinel guinea pigs exposed to the ward exhaust air for prolonged periods (8). There have been a few other examples of known pathogens collected from spaces with infected workers or materials (packing plants, goat hair sorting, etc.). In no case has the recovery of airborne pathogens been linked quantitatively with the incidence of disease. At this time, the Communicable Disease Center does not recommend prospective sampling of hospital environments

but relies on maintenance of clean environments and retrospective epidemiological data for confirmation of control efficacy (6). The FDA in their Good Manufacturing Practice Guides for Pharmaceuticals and Parenteral Solution Preparation does require air sampling in the work place. Their concern is with *all* particulate contamination that may enter the product. Microbial sampling alone as described by Kraidman (5) and Fincher (2) may not meet this requirement.

We do have many of the tools for monitoring a work place where the type and approximate concentration of a pathogen is known or suspected. Improvement is needed, but this should not be a total deterrent to monitoring aerosols and developing needed information on observed, expected, and, as the data base permits, a rational expression for an "allowable" microbial concentration.

Since publication of the following (extracted) material, two new samplers have become available. The first is a small portable battery operated sampler that can be useful in a variety of areas where the noise of an air mover is undesirable or it is necessary to move the sampler often. The "RCS" unit is essentially a straight vane centrifugal blower wheel about four inches in diameter with the fan scroll case totally surrounding the rotor. A special flexible strip of plastic containing pockets of nutrient agar is slipped into a slot in the scroll case to provide a liner for the housing. Thus, air is drawn through the rotor center at about 40 liters per minute and the particles are swirled out by centrifugal force to impinge on the agar surface lining the housing. The rotor is battery driven by four D cells and the entire device is approximately the size and appearance of a four cell flashlight. Although there are some limited data on efficiency, most of it indicates the samplers yield results comparable to the slit-impinger or the sieve sampler. Some reports show overall higher collection efficiencies than are seen with these well-known samplers. The strip bearing the collecting medium (agar with special nutrients added to meet unique sampling requirements) is available from the suppliers in sterile packaging. A colony counting device is also available. The sampler is simple in concept and should be reliable in operation. Its simplicity and lack of need for pumps and external power enhance its appeal for sampling in relatively inaccessible

locations. It does not yield data on particle size of the aerosols collected as does the Andersen sampler, nor does it provide time-concentration data as does the slit impinger. In concept it might be considered an advanced modification of the centrifugal sampler developed by W. F. Wells in 1933 (9)(10). Although not advertised as such, it can be used for sampling particulates onto surfaces for morphologic or chemical analysis. The limitations cited above suggest that further research be applied to this sampler.*

The second microbial aerosol sampler, only recently available, is the "Microban" Air Sampler (Model AS-101). This is a pump, single stage sieve collector and timing device package in a small baggage type container. It uses a standard 100 x 15 mm plastic petri dish and requires only connection to 100 VAC power for operation. The device most simply resembles a single stage Andersen sampler with sieve holes of 0.014" diameter closely approximating the 5th stage of the Andersen (0.0135 D holes). At the stated sampling rate of .01 M³/minute the sampler should impinge 1.5 to 2.0 μ m and larger samples directly onto the nutrient agar. The sampler is simple, small, light, and quiet. It would appear to be most useful in sampling air in relatively clean intramural environments. Although performance data are not available, the sampler should have the efficiency and characteristics of the Andersen sampler or the "sieve" sampler described in PHS Monograph No. 60.**

*This device is available from Folex-Biotest-Schlussner Inc., 60 Commercial Avenue, Moonachie, New Jersey 07074.

**It is available from Ross Industries, Inc., Midland, Virginia 22738.

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SAMPLING AIRBORNE MICROORGANISMS

Mark A. Chatigny

The authors consider Mark Chatigny's chapter on Sampling Airborne Microorganisms—from the 5th Edition of *Air Sampling Instruments*, 1978, M. Lippman ed.—an excellent state-of-the-art treatise. Accordingly, and with Dr. Chatigny's kind permission, we herewith include his chapter. We have edited the introduction he authored especially for this book, but have not altered the excerpted section.

INTRODUCTION

In response to a rapidly increasing awareness of problems in air pollution and air hygiene, considerable emphasis has been placed on sampling of gaseous and particulate contaminants. Although included in the latter category, airborne microbes have not been considered major air pollutants as have chemical aerosols. They have been of some concern in extramural environments (e.g., plant diseases) and of considerable interest in intramural (e.g., hospital surgical theaters) environments.

The intrinsic characteristics of microbes make them difficult to collect and assay quantitatively. The collection instrumentation available tends to be less sophisticated, though no less diverse, than that for other particulates and to require more processing after collection. There are few standard devices for sampling and virtually no standards for allowable or desirable microbial burden of the air. The most frequent practice in sampler selection is to review the literature in a particular area, select a system shown to work in circumstances similar to those expected and modify it as deemed necessary. There is nothing wrong with this approach, although it is a bit laborious for the air hygienist who may be more concerned with defining an ambient condition than in developing new techniques. The general purpose of this section is to point out some of the major problems to be expected, to provide leads to the work of others in the field and to develop a rationale for selection of samplers requiring minimal modification. Public Health Monograph No. 60 (1) covers a great deal of basic information and

equipment description which is almost a prerequisite for selecting a sampling system, although many of the equipment descriptions are now somewhat dated. Items F1, F2, F3, and F4 contain excellent detailed data and basic principles of more recent devices used for sampling airborne microbes. Chapter 4, by Akers and Won in *An Introduction to Experimental Aerobiology*, one of the selected references listed in "Selected Reviews and Monographs" below, contains an excellent review of the subject, comparisons of efficiency of equipment and methodology for assay of data collected.

Table I-43 provides some suggestions for selection of samplers, considering only a few of the most widely used samplers and a limited set of "typical" sampling problems. Many more of the particles collection devices discussed in this volume will also be usable and are discussed further below.

Background

Sampling for airborne microorganisms does not differ from ordinary particulate sampling except for the added necessity of assessing viability of the microbes of interest. Although sampling for allergenic materials, usually proteinaceous, is similar in many respects, discussion in this section will be limited to the requirements for sampling atmospheres for living microbes.

Much of the technology of sampling of airborne microbes has been developed by medical researchers concerned with both the viability and infectivity of the airborne microorganisms in

Table I-43
SAMPLERS MOST FREQUENTLY RECOMMENDED FOR USE IN
SAMPLING MICROBIAL AEROSOLS

Sampler	Principle	Sampling Rate 1pm	Sampling Time	Application
Andersen multi-stage sieve-type ^(A,1)	Impact on nutrients	28.3	1 min Min.* 20 min Max.	Bacteria and viruses. Low to medium concentration aerosols
Andersen 2-stage disposable sieve-type.	Impact on nutrients	14-28.5	1 min Min.* 20 min Max.	Collect CFU unless surfaces are washed into medium. Provides particle-size data.
AGI-30 raised jet all-glass impinger ^(A,2)	Impinge into fluid	12.5	ca. 15-60 min. Max.	Bacteria, viruses, etc. will work on wide range of concentrations.
Large volume electrostatic sampler (LVS/2K) (LVS/10K) ⁽³⁾ , (LEAP) ⁽⁴⁾	Combination electrostatic and impaction into fluid	500-10,000	Unlimited (Fluid may be recirculated w/some makeup)	Bacteria and viruses. Collects into fluids and counts total viable unit. Efficiency 60-95 of ACI-30.
Multiple slit impinger (MSI) ⁽⁵⁾	Impaction	1,000	Same	Same
Membrane filter ⁽⁶⁾	—	5-50	“Minutes” for bacteria and virus. Longer for spores and fungi.	Primarily hardy spores but can be used for bacteria and viruses.
Slit sampler ⁽⁶⁾	Impaction	28.3	1 min. to 1 hr.	Provides time-concentration. Collects CFU. Limited concentration range.
Open Petri dish with nutrient agar		—	0-4 hrs.*	Biased to collect large particles (CFU)
Open settling surface uncoated.		—	Unlimited	Same as above, collects hardy spores.
Hirst spore trap ⁽⁷⁾	Impaction	10	24 hrs.	Spores and pollen collected outdoors.

Table 1-43

**SAMPLERS MOST FREQUENTLY RECOMMENDED FOR USE IN
SAMPLING MICROBIAL AEROSOLS (Continued)**

Sampler	Principle	Sampling Rate lpm	Sampling Time	Application
Multi-stage liquid impinger ⁽⁶⁾	Impingement	55	Varies	Collects individual cells gently at moderate flow rates with size selection similar to respiratory tree.

* May be extended by use of OED wash. See Reference 52.

A Recommended as "laboratory standard" samplers.

(1) 2000 Inc., 5899 South State Street, Salt Lake City, Utah 94017.

(2) Ace Glass, Inc., Vineland, New Jersey 08360.

(3) Litton Systems, Inc., Applied Science Division, 2003 East Hennepin Ave., Minneapolis, Minnesota 55413.

(4) Environmental Research Corp., 3725 North Dunlap Street, St. Paul, Minnesota 55112.

(5) Gelman Instrument Co., 600 South Wagner Road, Ann Arbor, Michigan 48106; Millipore Filter Corp., Bedford, Massachusetts 01730.

(6) New Brunswick Scientific Co., Inc., 1130 Somerset St., New Brunswick, New Jersey 08903.

(7) C.F. Casella & Co., Ltd., Regent House, Britannia Walk, London N.1, England.

(8) A.W. Dixon & Co., 30 Anerly Station Road, London S.E. 20, England.

growth media, cell culture, or in suitable *in vivo* host systems. Infectivity may lead to pathogenic response, and this parameter has been of interest in studies of intramural air hygiene which have ranged from contagion of such diseases as measles (2) to more recent studies of methods for control of airborne infection in surgical theaters (3) and wards, and even nuclear submarines (4). Air hygiene studies in laboratories have gained some interest based largely on the demonstration that virtually every operation with a suspension of microbes in the research or clinical microbiology laboratory can produce an aerosol (5) with particles in the respirable size range (6), and laboratory infections with every pathogenic agent studied have been recorded. The obvious connection is not believed to be mere coincidence.

Extramural air hygiene studies have been done. Workers have studied dispersal of microbes from sewage plants (7), airborne Q-fever virus from rendering plants (8), *Coccidioides immitis* from open ground (9), and rabies virus in bat caves (10). More frequently, extramural air sampling studies are of importance to workers concerned with transmission of animal diseases as recently reviewed by Hugh-Jones (11) or with plant infections (12). In almost every case, the strategy is to collect viable organisms by optimal means and to demonstrate their presence by ap-

propriate culture methods. Viability will be the parameter of primary concern in this section, and infectivity will be considered a response dependent on the host/parasite system used.

The major difference between indoor and outdoor microbial aerosols and their sampling requirements is that the outdoor aerosol particles collected will be of a wide variety from ill-defined sources, tend to be the hardy fractions of cell populations that have undergone relative humidity (RH) stress, ultraviolet (UV) irradiation and exposure to air pollutants, be hetero-dispersed, and usually require collection during an unknown variety of meteorological conditions. On the other hand, the indoor environment will have fewer types of infection sources and variety of microbes but more favorable environments for survival of the airborne microbes. It usually will have more airborne flora from human activity sources and will require sampling in still or low velocity air masses.

Factors to be Considered in Selection of a Microbial Aerosol Sampler

1. *The entire sampling system should be considered.* One should consider the objective of the work, the sampling plan, the proposed location(s) of samplers, the number of samples and the time period during which the samples are to be taken,

the effect of time variation on the cloud from which the samples will be collected, the techniques and logistics of the assay system to be used and what quantitation is required. The last two factors are of great importance since the biological characteristics of the sample can be far more variable than any of the physical or instrumentation factors involved. These factors, considered below in further detail with other important parameters, should be considered in a systematic manner.

2. *The sampler used should permit assay of the microorganism-bearing particles in a manner related to the end objective of the study.* For many purposes it is adequate to assume that one or more microorganisms exist per particle collected and, accordingly, one can relate the particles collected directly to colony-forming units (CFU). This is perhaps the simplest method of collection and it is usually done by impaction or settling deposition onto solid nutrient on which the microbes grow directly. In some cases it is desirable to have data useful for projecting total infective dosages, and it is necessary to evaluate the total number of viable organisms in a given volume of air. This type of sample is best collected into a liquid and dispersed in various dilutions onto growth medium for quantitative assay. Most microbe-bearing aerosol particles are readily dispersed in water with wetting agents, and individual cells will be counted. The latter technique is particularly useful if it is expected that the concentration of aerosol may vary widely. As examples of the above; if one is examining the intramural air of a hospital, it would be expected that a large fraction of the viable microbial organisms of interest would be of a limited variety of species borne at low concentrations on particles of dust, skin flakes, hair, or other detritus which would be deposited on surfaces of wounds or other susceptible areas. Sampling relatively large volumes of air for colony-forming particles would provide a reasonable assay of the infectious potential of the aerosol. On

the other hand, particles generated from some microbiology laboratory operations (e.g., centrifugation) have been shown to be within the respirable size range and frequently to contain several microorganisms as have those generated in sewage treatment plants. In these cases one might wish to sample at relatively low volumetric rates into liquids for assay of total viable organisms in the aerosol.

3. *The selected should meet the physical requirements of the application.* Sampling in a surgery may require a quiet-operating, large-volume sampler; sampling spores for plant pathogens in the extramural environment will require a low-power, robust sampler suitable for exposure to adverse weather conditions (e.g., the Hirst spore trap (13), see page O-12 of the 4th Edition), while sampling in a clean-room or spacecraft may require use of many sampling points using simple filtration devices (14). These are mentioned because too often one finds that workers attempt to apply laboratory devices to field situations, with attendant complications.
4. *The sampler should collect (and present) particles in the size ranges of interest.* More precise definitions of particle size and methods for measuring this parameter are given in sections F and G (4th Edition) of this text. With respect to humans and air hygiene problems, the respirable size range of 2-8 μm is perhaps the most important (15). These particles penetrate deeply into the lung and are retained in the nonciliated small passages and the alveoli for a sufficient period of time to initiate infection. The size is, of course, an aerodynamic particle size with an assumption of unity density. Less dense particles which may act aerodynamically the same, e.g., mycelia, dust particles, etc. ranging up to 30 microns, may be of equal interest for this reason. In the extramural environment, and frequently in the intramural environments with mechanical ventilation, the relatively high velocity of winds and turbulence of the atmosphere can keep rather large particles airborne for sustained periods of time. The protective effect of large par-

ticles against UV radiation may permit otherwise sensitive microorganisms to be carried great distances (16). Such protective effect may be a strong factor in reported incidents of extramural aerial transmission of Newcastle disease virus (17) and foot-and-mouth disease virus (18, 19). Other environmental factors (e.g., RH and air pollutants) were also considered in these epidemiological studies (11). Relative humidity, in particular, affects viability of airborne microorganisms markedly.

Various methods of fractionating sampled particulates by particle size are available and range from the simple liquid impinger used with a Porton pre-impinger or the size selective Andersen sampler to a variety of classifying devices employing impaction principles, charge-mass ratios, mass-area ratios (thermal precipitation), etc., (described further in other sections). The most practical method is that which is simplest, provides the needed data, and is consistent with other recovery requirements described here. Settling plates do not provide good overall size representation since they preferentially collect large particles, but they can be useful in many applications requiring knowledge of surface contamination from aerosols. The data collected do not represent aerosol concentration because it is related to specific particle sizes, air velocity and turbulence, sampling time, and other factors which must all be defined. If one knows or has good reason to postulate a particle size distribution (e.g., outdoor aerosols are most frequently log-normal as described by Junge (20)) one can infer an estimate of total concentration.

5. *It is desirable to know the expected aerosol concentration.* If one has a reasonable estimate of the range of concentration to be found, one can select a sampler that will have the necessary sensitivity and will facilitate the assay procedure. Concentration effects are most critical in direct impingement type samplers; e.g., the Andersen, sieve, or slit-type sampler where CFU counts greater than 200 or

250 per plate are difficult to count and in the case of the former sampler, prohibit the use of sampler "correction" table which correct the measured count in consideration of the possibility of multiple particles per hole area. Within a limited range (ca. 10:1), one can dilute the incoming aerosol with clean air, concentrate the aerosol if necessary (ERC collector-concentrator, Environmental Research Co., St. Paul, Minn.), or vary the time of sampling to control the quantity deposited. In the last case, one should be careful that the time is not made so short that the air clearance rate through the sampler becomes a significant fraction of the sampling period. Collection into liquid has the obvious advantage of readily permitting serial dilution for assay and accommodates a very wide range of aerosol concentration. Bubblers and impingers should not usually be used for prolonged periods (>30 min.) because of evaporation of aqueous collecting fluid, but continuous flow samplers can be used for longer periods.

6. *The wind velocity (and direction).* This parameter probably marks the single largest difference between intramural and extramural air sampling other than UV radiation. Sampling intramurally, one can expect low velocity airflow, rarely exceeding 100 lfpm (31 m/min) whereas extramural sampling may find the velocity ranging from 0 to 50 km/hr and direction changing radically. Intramural sampling of large size particles may be done with such simple devices as settling plates, and considerable variation is tolerable in the design of inlet configurations of samplers for particles of sizes below approximately 5 μm that are not greatly affected by anisokinetic conditions (21). On the other hand, sampling of particulates from a medium velocity airstream requires at least nominal isokinetic sampling, as discussed in Section L (4th Edition) and by others (22), if a representative sample is to be collected. Isokinetic sampling may be achieved by utilizing a sharp-edged nozzle pointing into the wind with natural wind through-

put, or pumps, as is done with the Hirst spore trap (See Section O-12, 4th Edition), by using air movers with filters in the stream, or by building an "isokinetic wind tunnel" from which the sample can be drawn (23). It may also be done by using a baffle to provide a "stagnation point" immediately above the sampler entry from which a sample can be collected (20)(22). May (24) has suggested that the stagnation point baffle, if used, should be as large as possible; since it then subtends a wide arc, it is relatively insensitive to direction.

In the extramural environment, directional control of the sampler may be as important as sampling isokinetically. Wind direction can change radically and rapidly, and the motion of a prevailing wind is somewhat misleading. Yaw losses are greatest when sampling large particles and when the diameter of the inlet nozzle is small (21). Particles greater than 10 microns cannot navigate sharp turns without heavy losses and must be sampled directly. For example, the AGI-30 sampler has a curved neck with a cut-off in this size range, and particles larger than 8 to 10 μm are recovered by washing out the inlet tube. Sampling of particles smaller than those from air velocities less than five MPH is probably not significantly affected by airflow direction.

7. *The biological characteristics of the agents sampled.* After the physical characteristics of the particulate matter have been considered in the sampler selection, the biological characteristics of the organisms and the collectate must be considered in the selection of the sampler, the media, the collecting time, and the storage of the collectate. It is the biological area wherein the most variability exists, and the considerations of relative sampling efficiency differences of 10 to 50% among samplers can be meaningless if one considers the not-infrequent 3 to 5 log biological variation. Numerically this may not be important if a qualitative measure of the aerosol is sufficient (i.e., simple detection of the presence of specific microbes). This may require col-

lection conditions optimized for the particular organisms. On the other hand, quantitative collection and recovery may require use of several types of samplers and processing techniques. Collection on filters or water-free surfaces is probably best limited to hardy bacterial spores that can withstand desiccation. This technique has been used in the detection of hardy spores of concern as models of contaminants on interplanetary vehicles (14). Fungal spores, similarly, can be collected on impaction plates, sticky surfaces, or electrodes, because they are so robust; (if viability/infectivity is not to be measured, the sample can be put onto nutrient medium or fluids with little damage, but it is important that the trauma associated with sampling (e.g., desiccation, osmotic shock, etc.) be minimized. When collecting directly onto nutrient, a rich medium is perhaps more effective than one which will permit differentiation by species through limitation of growth of non-desirable organisms. The use of rich collection media will permit growth of undesirable material, and for most bacterial sampling a compromise using such additives as a fungicide (amphotericin B), or similar materials will usually be required to prevent overgrowth by molds and fungi. Subsequent transfer of viable colonies to selective media will aid in classification and identification. If spores are sought, the collection may be heat-shocked before adding further nutrient materials, and the irrelevant nonsporulating bacterial burden will be reduced substantially. Noble (25) has discussed assay techniques at some length. Viruses pose some rather unique problems in sampling. The interest in sampling aerosols of viruses has increased rapidly in recent years, and the technology accordingly has become more diverse. Many of the methods for sampling bacteria are useful but are complicated by the requirement for a viable substrate for virus replication. Because sampling for viruses is a relatively recent development it will be discussed in further detail below.

Infectivity has been noted above in its

broadest terms and related directly to viability. In most cases, infectivity must be related to an *in vivo* host system. Most simply, it can be measured by using sentinel animals, and this technique has been successful where others have failed (26). If this is not desirable or possible, perhaps due to requirements for extended collection times, then inoculation of suitable host animals with a concentrate of a liquid collectate may be done. However, there is no substitute for aerogenic infection procedures, and if the objective of the sampling is to evaluate respiratory infection potential, the resultant "aerogenic" infectious dose should be evaluated with some caution. Intranasal instillation has been shown to be an excellent substitute for direct aerosol challenge in some cases and abysmally poor in others but is perhaps the nearest approach to aerosol challenge in determining dose response.

8. The "efficiency" of the sampler. This is discussed as a parameter only to emphasize its ephemeral character. The below extract from remarks by Gregory (27) serve well to emphasize some of the problem areas.

"Under simple conditions it is not difficult to define a standard for air sampling. With nonaggregated spores of one species liberated in a wind tunnel, isokinetic sampling through a feathered orifice facing up-wind collecting into a suitable membrane filter with precautions against overloading should give a reliable estimate of the number of particles in a measured volume of the air. The cascade impactor, catching on a thick layer or soft adhesive, tends to reveal spore clumps intact; and if this feature is undesirable, the liquid impinger should be used to break up aggregates. The more varied the population in species, particle size, state of aggregation, the harder it becomes to measure the concentration in the air."

In addition, this warning succinctly advises against "comparison of results broadly." Efficiency of particle collection should be maintained but not at the

cost of changing the particle characteristics or if viable loss of viability or infectivity is the characteristic of interest. As an example, the 0.4 μm Millipore filter as an air sampler of small particles may be somewhat more efficient than the liquid impinger (AGI-30), but viable recovery will usually be lower except in the case of hardy spores or fungi. Similarly, the Litton (LVS) high volume sampler is from 40 to 70 percent as efficient as the AGI-30, but it has a sampling rate approximately 100 times the AGI. Selection of a sampling device must include consideration of these efficiency factors. Considering the range of biological variations discussed previously, the absolute efficiency of the sampler as a particle collector is not usually the most important parameter and comparison of overall efficiencies of collecting living microbes is probably valid only for single species and strains of microorganisms and defined growth media and conditions.

SAMPLING VIRAL AEROSOLS

Background

For the most part, virus aerosols originating from natural sources, i.e., humans, hospital activities, animals, etc., tend to consist of relatively large particles (28)(29)(30). Those from laboratory operations have been shown to be in the respirable size range (5)(6)(31) and to contain some particles with single virions. A great deal of energy coupled with a very high titer virus suspension at the source (ca. 10^{12} - 10^{16} /ml.) is usually required to generate concentrated aerosols of viral particles in the submicron particle size ranges. While the likelihood of single virion particles is not great, there are occasions when they will be found. For example, in the operation of zonal centrifuges where virion particle counts as high as 10^{12} (32) or more per ml are being concentrated, a leakage may create an aerosol with a mass median diameter (mmd) of 1-3 μm but with large numbers of single virus particles. The same has been shown to occur to a much lesser degree in the output from a cough or a sneeze (28). Since the electron microscope count of virus particles is frequently four or more logs higher than that of plaque-forming (or infective) units (this may be an artifact of

the infectivity assay system), multivirion particles in the respirable size range or larger should be considered of primary interest. For the most part this relieves one of the difficult tasks of sampling submicron particles. Accordingly, most of the physical factors discussed previously with respect of sampling bacteria are applicable to viral aerosols, and most of the devices useful for collecting bacterial aerosol samples will also be useful for collecting virus-bearing particles. This was amply demonstrated by the early work of Meiklejohn, et al. (33) who sampled large volumes of air in a smallpox hospital and recovered virus on very few occasions using the impinger sampler. When, in other experiments, settling plate samplers were added, the virus was recovered in particles of large equivalent diameter (34).

The biological response of virus particles to sampling can vary widely and be quite different from that of bacteria. It has been demonstrated (35) that humidifying the air immediately before collection into an impinger can yield recovery of T₂ coliphage increased by as much as three logs over than from an impinger alone. On the other hand, other studies (36) showed that presampling humidification decreased the recovery of mengovirus 37A and vesicular stomatitis virus. The latter is a lipid-containing virus which has been reported to be inactivated rapidly at high RH. Although generalizations are hazardous, the work of many aerobiologists shows that airborne viruses are at least as sensitive to different relative humidities as are bacteria. DeJong and Winkler (cited by Benbough (37)) concluded that viruses with structural lipids generally survived best in aerosols at low humidities while those without structural lipids generally survived best at high RH's. These conclusions have been confirmed by Benbough (37) who attempted to isolate this effect from that of composition of suspending fluids and sampling methods.

The selection of the air sampling technique will be affected by the desired observations. This may include infectivity for animals or tissue cultures as opposed to morphological observation by electron microscopy. In the former case one would be concerned with micron-size or larger particles while in the latter case, it may be necessary to collect submicron size particles. In the final analysis, the overall probability of infection can only be assessed by the viable or

infective dose recovery, as well described by Noble (25) and by Akers and Won (38).

Review of Sampling and Assay Methods

A simple settling chamber technique was devised by Hankings and Hearn (39). They sampled VEE virus from aerosols containing as few as one plaque-forming unit (PFU) per liter of air by drawing the sampled air through serial cell culture flasks at rates up to 1.0 liter/min.

Impingers using tissue culture nutrient with added serum, antibiotics and antifoam agents (Tween 80, Dow Corning, etc.) and a variety of other fluids have been used successfully in collection of Coxsackie A₂₁ (40), Simian virus 40 (41), vaccinia, influenza, VEE and poliomyelitis (42). Some of the hardy viruses (e.g. coliphages) have been successfully collected on paper, Millipore, and Nucleopore filters and subsequently transferred to suitable growth medium (43)(44).

The slit sampler has been used (45)(46) with a 12% gelatin collecting medium which was subsequently liquified by heating to 37°C and poured onto cell mats. It was also used with agar and the collectate washed off the agar onto the cells (42). These media were employed to avoid the damage to sensitive cell culture mats from drying in the sampling airstream. Recovery from such media is often hampered by retention of the virus particles in the agar (43)(47). Jensen (43) found improved recovery with this technique if he coated the agar with skim milk.

The Andersen sampler has been used for sampling viral aerosols using similar collecting techniques. Guerin and Mitchell (48) used a collection medium of 3% gelatin with added antibiotics and melted this (37°C) onto cell culture mats. Thornley (49), on the other hand, simply cut out a disc of agar after sampling and placed this on the cell monolayers. This may be an oversimplification for sampling-sensitive viruses. In an improvement on such techniques, Thomas (50) used a mixture of sucrose, glycerol and bovine serum albumin on raised discs in the Andersen sampler (and in a slit sampler). By his technique, Thomas was able to sample for periods up to one hour with this modified Andersen unit. This sticky surface provided good recovery in the laboratory of polio, vaccinia and Semliki Forest viruses. In the field he recovered rabbit pox virus (51). Incidentally, it was observed that

laboratory-generated aerosols showed a preponderance of particles collected on the fifth and sixth stages of the Andersen sampler, while the field-collected aerosol appeared upon the first three stages. Although these adaptations of the Andersen sampler provide increased total sample volumes over impingers and impactor-samplers used with plain agar (usual flow 12 to 30 lpm with 30 min max. sampling time), there is frequently need for much larger sample volumes in air hygiene studies to evaluate very low aerosol concentrations. The Andersen type sampler can be used for only limited times due to agar drying. May (52) has suggested that the use of 0.2% oxyethylene docosanol (OED) emulsion poured over the dry agar surface and allowed to soak in for a few seconds retards evaporation by as much as fivefold in two hours and almost twofold in six hours. Colony counts on tryptone agar with 0.2% OED in the Andersen samplers run as long as 7-1/2 hours showed increased counts of the first two stages.

The LVS (Litton) sampler (1000-2000 lpm) has received increased attention in recent years. Gerone, et al. (28) used this sampler with Eagle's Basal Medium with added calf serum and antibiotics to collect Coxsackie A-21 virus. Arntstein, et al. (53) recycled the collecting medium through the LVS in sampling for human respiratory disease pathogens. Hugh-Jones, et al. (17) used the LVS with peptone water containing penicillin G, (5,000 units/ml) in conjunction with a fungicide for recirculating through the sampler during a 60-min. sampling period. They demonstrated that the Herts, 33/56 strain of Newcastle disease virus (NDV), recirculated for a 60-minute period, suffered no significant viable loss. Larson, et al. (54) used the LVS in laboratory studies of small particle Rauscher leukemia virus (RLV) aerosols and in their studies of natural aerosols. The collecting medium was tissue culture broth medium of "Hanks' balanced salt solution" with 10% fetal calf serum added. Laboratory studies have shown the LVS to be comparable in efficiency to the AGI sampler in collection of viruses from deliberately generated aerosols, although in sampling animal rooms in which RLV-infected animals were held, no virus was recovered from the LVS samplers. Winkler (10) used this sampler to recover rabies virus in bat caves after being unsuccessful with several other techniques. In recent work, Chatigny and Biermann (55) have used a steam-injection mod-

ification of the cyclone separator described by Errington and Powell (56) for collection of aerosols deliberately generated to produce single virion-bearing particles in the submicron size range. The T₃ bacteriophage used was plated directly with *Escherichia coli* from the water collectate.

SAMPLER SELECTION

Only two samplers have been suggested as standards (by a learned committee (57)); the all-glass impinger, with or without the Druett-May pre-impinger, and the Andersen sampler (58). Although the six-stage sampler has been described, the two-stage, "disposable" Andersen sampler which fractionates the sample into respirable (2-8 μm) and nonrespirable (> 8 μm) sizes can also be considered a "standard," particularly since it incorporates the hole-spacing components. Although it suffers from the same limitation of concentration range that affects the six-stage unit, it is economical and can provide adequate data for many studies. The samplers listed in Section O (4th Edition) of this volume are, almost without exception, usable for sampling microbial aerosols. Some will require adaptation to meet specific needs. The Milipore filters described in Section N (4th Edition) and the precipitators listed in Section P (4th Edition) can be used. The LEAP sampler (Environmental Research Co.), the Electrostatic Bacterial Air Sampler (Gardner Associates) and the above-mentioned LVS sampler made by Litton Systems, Inc., are all usable in particular applications. Although references have been made above to the application and use of the LVS, which has an electrostatic charge principle as its major mode of collection, the multiple slit impinger (MSI) sampler (59) (see page O-13 of 4th Edition) is being used more frequently and should be considered equally acceptable. It is considerably less subject to electrical and mechanical failures than the electrostatic charge-based devices. The electrostatic charge units do not function well in outdoor environments of high humidity conditions and must be considered primarily laboratory tools; further, the effect of corona-discharge on sensitive microorganisms is not well defined, and the MSI sampler may yield a higher viable recovery in some cases.

There are cases wherein a novel method may be necessary. Without fully reviewing the sampler development literature, it can be stated

that in recent years developments have been directed toward large volume sampling and some classification of the particles on the basis of size or density to facilitate assay after collection. The simple cyclone, similar to those described in Section O-31 (4th Edition), has been made up in a size to sample 80 to 150 lpm (56) and modified (55) to collect submicron particles. A similar liquid scrubber device had been reported (60). Modifications of the May three-stage sampler and of the Andersen sampler (50) have been described. These extend the size selection range to more than 20 μm in recognition of the needs of intramural sampling. A simple "man-operated" filter-type sampler has been reported (61) as have variations of the "rotorod" (62) collector modified to collect a wide spectrum of particle sizes (63). An even simpler electrostatic rod collector, described some years ago (64), permitted collection of particles and subsequent deposition on a nutrient surface. No quantitative comparison data are available for these devices.

Recovery and growth on suitable media, as described previously, is the usual procedure for sample assay but other methods, usually more complicated, can work as well or better to meet special requirements. Analysis of the collectate by such techniques as fluorescent antibody staining (65), chemiluminescence (66), protein content, or a wide variety of techniques described by Strange (67) can permit use of the best features of particle selection equipment, electrostatic collection, sticky-strip collection, settling plate samplers, or even the simple charged glass rod. Most of these methods are discussed in one or more of the several books or monographs listed below. However, whenever possible, well-calibrated commercial equipment and well tested assay procedures should be used, if for no other reason than that there is usually a good body of data on the expected performance. Table I-43 and selected references listed below in conjunction with catalogue sections of this book, should provide the worker with adequate information, either to conduct a sampling program or to become sufficiently aware of research areas and apparatus availability to define the needs for special techniques.

Equipment catalogued and commercially available has grown mightily in 15 years. Nevertheless, there is still room for the use of simple

self-devised techniques to meet special requirements. The reader is advised to look not only at those devices listed as "microbial aerosol samplers" but to examine any of the particulate aerosol samplers with an eye toward his own application. It is the writer's opinion that most should be afforded some method of calibration, usually with laboratory-generated aerosols closely simulating those to be sought.

The vigorous assistance of Ms. Doris Clinger and Dr. H. Wolochow in preparation and review of this section is most gratefully acknowledged.

SELECTED REVIEWS AND MONOGRAPHS

Material in each of the texts listed below will be found helpful. They are listed by title and author/editor, then chapters of particular interest.

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K. R. May: Physical aspects of sampling.
W. C. Noble: Sampling airborne microbes; handling the catch.
R. E. O. Williams: Spread of airborne bacteria pathogenic for man.
D. A. J. Tyrrell: The spread of viruses of the respiratory tract by the airborne route.
2. The Microbiology of the Atmosphere, 2nd Edition. P. H. Gregory. In particular, Chaps. IX, XI, XIV, XV and XVIII. John Wiley and Sons, New York (1973).
3. An Introduction to Experimental Aerobiology. R. L. Dimmick and A. Akers (eds.), Chaps. 4, 11, 12, 17. John Wiley and Sons, New York (1969).
4. Particulate Clouds: Dusts, Smokes and Mists. H. L. Green and W. R. Lane. In particular Chaps. 7, 9, 10, E. and F. N. Spon, Ltd., London (1964).
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EPIDEMIOLOGY

EPIDEMIOLOGIC PRINCIPLES AND METHODS FOR OCCUPATIONAL HEALTH STUDIES

Carl M. Shy

A. DEFINITIONS AND USES

Definition and Scope of Epidemiology

Epidemiology is a study of the occurrence and distribution of disease in populations and of the factors that account for this distribution. Epidemiology shares with experimental and clinical medicine the overall objective of understanding causes of human disease. These three basic approaches to the study of human disease differ by the methodology each employs.

Experimental medicine, including the disciplines of microbiology, biochemistry, physiology, pharmacology, experimental pathology, and other basic medical sciences, utilizes the controlled experiment to test hypotheses about causal agents and disease mechanisms. It works with experimental models of human disease processes and brings to bear the powerful methods of controlled manipulation of variables and replication of results by different investigators. The greatest limitation of the experimental method is that it approaches the complex reality of human disease by isolating one variable after another within a framework of extremely simplified assumptions. This "scientific reductionism" often leads to conclusions that are removed from the overall causal chain of disease in man.

Clinical medicine and epidemiology, on the other hand, begin and end with disease in man, and both are more observational than experimental disciplines. Clinicians are concerned with individual diseased persons. They seek to diagnose the underlying disease that is causing the combination of symptoms, observable signs, and physiological and biochemical abnormalities detectable in affected individuals and to alleviate or mitigate the disease process or at least the pain and disability accompanying the disease. The

clinician makes his diagnosis by gathering enough evidence about the patient to exclude all but one of the several disease entities that might account for the complex of clinical findings.

This reasoning process is largely based on empirical evidence reported in the medical literature and on an understanding of pathophysiologic mechanisms, rather than on general theories such as are available in the physical sciences. But the clinician's observations are based on a highly selected segment of the population, namely, those persons who seek medical attention. These persons are not necessarily representative of the population affected by occupational exposures.

Unlike the clinician, the epidemiologist does not usually have access to a wide array of clinical and biochemical information about a sick person. His immediate concern is not why an individual may be sick, but why disease frequency differs from one population to another, or from one time to another in the same population. The focus of epidemiology is with risk factors, often extrinsic to the sick person; it seeks to identify and quantify relationships between population groups at high risk and factors in the community or work environment that might account for the high risk.

Each of the three disciplinary approaches makes important and complementary contributions to our knowledge of human disease. The experimenter addresses disease mechanisms in an appropriate experimental mode, the clinician investigates disease manifestations in sick individuals, and the epidemiologist studies community determinants of disease risk. Disease treatment and prevention must be approached from each of these points of view, and the findings of one discipline can often lead to progress in the others.

Occupational Epidemiology

Occupational epidemiology is a study of the occupational environment as a risk factor for disease in working groups. The occupational setting is also used by the epidemiologist to obtain convenient access to populations in order to study coronary heart disease, bronchitis, high blood pressure, and other diseases that may not necessarily be primarily related to the work environment. The methods of occupational epidemiology are not generically different from those of acute or chronic disease epidemiology, but special features of the work environment are particularly beneficial to the epidemiologist. Some major advantages of occupational (group) epidemiologic studies are:

1. Complete plant populations can be readily constructed for previous years of employment.
2. Detailed individual exposure histories can sometimes be constructed from employment records.
3. In some plants, recurrent medical examinations provide sequential information on the health status of employees.
4. The vital status of an entire employment roster can be ascertained historically through retirement-insurance plans (though in many cases these plans cover only the vested worker).
5. In some plants, a single chemical dominates the exposure history of an occupational group, as in the case of vinyl chloride, nickel, chromates, asbestos.
6. Case-control studies conducted within a plant population can be referred back to a known population base, thereby allowing the investigator to obtain absolute estimates of risk and to evaluate the representativeness of the case and control study groups.

These features of occupational studies are important in the epidemiological approach to disease etiology. There are relatively few similar population settings in which the epidemiologist can as easily completely enumerate a cohort retrospectively, obtain detailed historical information on individual exposure, and simultaneously determine the vital status of the cohort. Much of our knowledge of chemical carcino-

genicity in man has originated in studies of occupational cohorts.

A notable disadvantage of occupational studies is the fact that employed populations are usually healthier than the general population and, therefore, provide a biased representation of the true occurrence of disease in the entire community.

Uses of Epidemiology in Occupational Medicine

The occupational physician must depend on the skills of the clinician to detect disease occurrence in workers, but he needs the discipline of epidemiology to relate disease to factors in the occupational environment. To the extent that occupational medicine is concerned with prevention of hazardous occupational exposures, its basic science is that of epidemiology. There are, of course, other responsibilities requiring administrative and in some cases toxicological expertise, but insofar as the occupational physician wishes to approach his responsibility of disease prevention scientifically, he should be able to apply epidemiological methods in his practice. Unfortunately, the training of occupational physicians in the past failed to emphasize a rigorous curriculum in epidemiology and the related quantitative tools of the biostatistician.

Several uses of epidemiology have been described in the classical treatise by J. N. Morris (21). Among the uses most relevant to occupational medicine are the following, adapted from Morris' more generalized description:

1. To search for causes of disease and injury by comparing work exposures or other hazards of different occupational groups.
2. To study the history of disease patterns in occupational cohorts, describing changing patterns and possibly the changing character of disease, with a view to relating these changes to production and work processes.
3. To diagnose the health of the community of workers that fall under the purview of the occupational physician; to measure the magnitude and distribution of disease in terms of incidence, prevalence, disability, and mortality; to set occupational health problems in perspective

against other risk factors; to identify subgroups that require special surveillance and medical attention.

4. To evaluate the effectiveness of occupational health services with a view to an improved allocation of scarce medical resources, elimination of unnecessary practices, and introduction of new procedures that can be used to assess disease risks.
5. To identify new disease syndromes or disease entities related to the introduction of new agents or processes in the work environment, e.g., mesothelioma and asbestos exposure, angiosarcoma and vinyl chloride exposure.
6. To account for the entire spectrum of occupational disease risks, from the earliest preclinical manifestations in exposed workers to the development of latent disease excess by (a) including workers from first employment through those retired for many years; and (b) by following the course of disability and disease from first occurrence to subsequent etiology of a disease process.

As noted by Morris, these uses derive from the principle that epidemiology is a study of disease distributions and of the determinants of differences in these distributions in population groups. In systematically gathering information on disease distributions in occupational cohorts, the occupational physician has the opportunity to assess risk factors, evaluate occupational health services, describe changing patterns of disease in relation to work practices, and diagnose the health status of "his community." Epidemiology provides the practitioner of occupational medicine with the principles and methods to make valid assessments of possible associations between occupational exposure and disease risk.

B. EPIDEMIOLOGIC STRATEGIES, INDICES OF DISEASE AND MEASURES

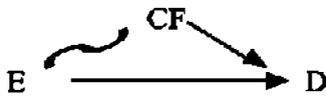
General Notation

- E = exposure or study factor, or persons exposed
 \bar{E} = absence of exposure, or persons

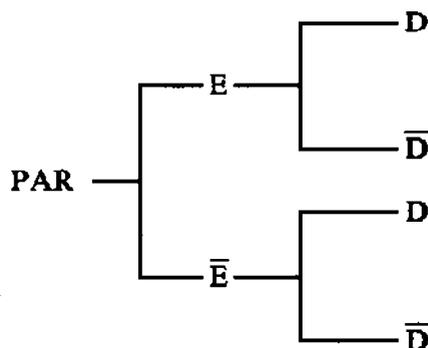
- not exposed
D = disease or death
 \bar{D} = absence of disease or death
PAR = population at risk
N = size of the study population
n = size of a subgroup in the study population
RF = a risk factor for disease, other than the study or exposure factor
CF = a confounding factor (to be defined subsequently)
EM = an effect modifier
I = incidence of disease
CI = cumulative incidence
ID = incidence density
Pr = prevalence of disease
r = rate of disease
P(D/E) = probability of disease, given exposure
RR = relative risk, the ratio of disease incidence in exposed to incidence in nonexposed
AR = attributable risk, or the difference in disease incidence in exposed and incidence in nonexposed
PrR = prevalence ratio, or the ratio of prevalence in exposed to prevalence in nonexposed
OR = odds ratio, an estimate of the relative risk
SMR = standardized mortality ratio (based on indirect adjustments for the distribution of other risk factors)
SRR = standardized mortality ratio (based on indirect adjustments for the distribution of other risk factors)
→ = implies a causal association between a risk factor and disease
~ = implies a noncausal association in the distribution of two (risk) factors

Epidemiologic Strategies

The basic strategy of epidemiology is to establish an association (if one exists) between the distribution of group exposure to a study factor (E) and the distribution of disease (D), controlling for the presence of extraneous factors (CF = confounding factor) which may confound the relationship between D and E.



Symbolically, the epidemiologist works in the following framework:



Assuming that exposure and disease can be simply dichotomized, the framework of an epidemiologic study can be reduced to a 2 x 2 table:

	E	\bar{E}	
D	a	b	m_1
\bar{D}	c	d	m_0
	n_1	n_0	N

where m_1 is the number of persons diseased, m_0 the number without disease, n_1 the number exposed, n_0 the number unexposed, a the number of exposed persons with disease, b the number of unexposed persons with disease, etc.

If confounding factors are present, a separate 2 x 2 table must be constructed for each level of the confounder. For example, in the study of asbestos exposure (E) and lung cancer (D), a separate 2 x 2 table would be made for

cigarette smokers and nonsmokers if smoking habits were unequally distributed between asbestos workers and others (and thereby created a situation of confounding). Confounding is controlled by stratification on the confounding factor, as will be discussed later.

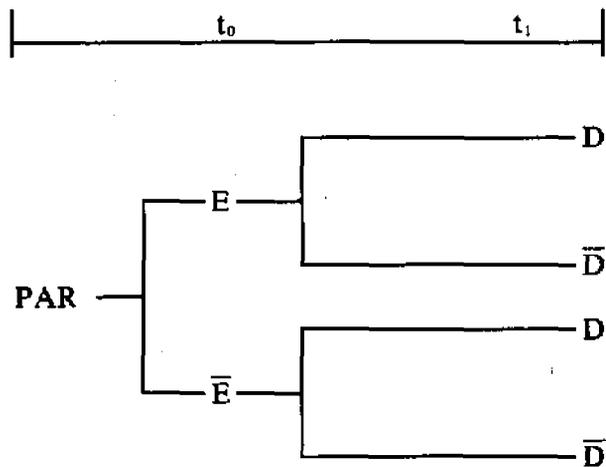
The initial step in an epidemiologic study of a work environment is to *describe* the distribution of disease (or functional impairment) among the working population of a plant or industry, without as yet postulating that a causal relationship exists between the work environment and disease. Thus, in the early studies of rubber workers (16) and steel workers (12), the investigators attempted to measure whether any specific disease excess could be found in the total cohort. These initial descriptive studies have their place in *generating hypothesis* for subsequent study, but they lack the necessary specificity and scientific rigor of hypothesis-testing investigations. Descriptive studies are of use in identifying high risk groups (e.g., cigarette smoking asbestos workers); in detecting temporal changes in disease frequency that might suggest causal agents; and in demonstrating whether there are geographical differences in disease distribution that might subsequently be explored for etiological significance. Descriptive studies are by nature epidemiologic "fishing expeditions" in which the first clues to population differences in disease distribution are obtained as warning signals that certain groups, places, or times deserve special attention. In some cases, clinical observations on disease clusters within a plant may raise the level of concern, but these observations need to be confirmed by some form of descriptive epidemiologic study in which disease frequency can be related to the working population at risk and compared with "expected" disease frequency.

The next phase of epidemiological investigation is the *analytical study*, designed with a specific testable hypothesis in mind. For example, is leukemia among rubber workers related to solvent exposure? Before an analytical study is initiated, the investigator must have a biologically plausible basis for postulating an association between E and D, and must usually have positive results from a descriptive epidemiologic study suggesting that a specific disease or cause of death is likely to be associated with a particular exposure. Analytical studies are definitive to the degree that they measure and

control for other known risk factors, but in the early stages of etiologic investigations it is often difficult to obtain detailed information about all the risk factors of interest. Thus, epidemiologic inferences are broadened usually by replication of results under different circumstances and by different investigators. This "consistency" characteristic of analytical epidemiology plays a key role in the extension of epidemiologic hypothesis to broader population groups, as will be discussed in the final section of this chapter.

In addition to the descriptive or analytical nature of epidemiologic investigations, three basic epidemiologic study strategies can be identified. These strategies are distinguished by the temporal sequence in which exposure and disease characteristics are ascertained by the investigator.

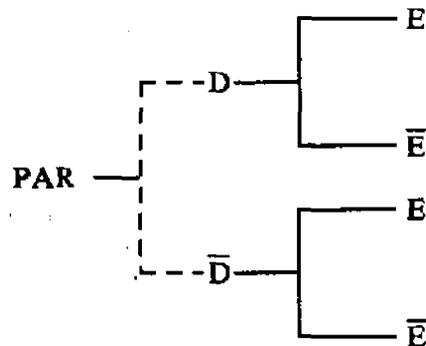
1. The *cohort study* is a longitudinal progression in time from exposure to disease occurrence in populations at risk. Schematically, this approach is:



where t_0 is a time clearly preceding the occurrence of disease when exposure characteristics of the PAR are known, and t_1 is a subsequent time when new disease events have occurred in the E and \bar{E} populations.

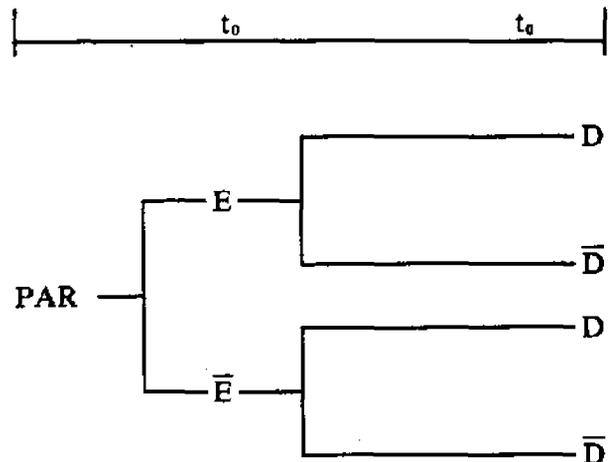
2. The *case-control study* is a retrospective progression from disease occurrence to exposure characteristics in D and \bar{D}

groups, usually without knowledge of the frequency of E or D in the source population at risk. Schematically:



The case-control study begins with the selection of cases and controls (without knowledge of absolute disease frequencies in the PAR). Subsequently, exposure and other risk factor information is sought for cases and controls.

3. The *cross-sectional study* consists of a simultaneous characterization of exposure and disease in a population at risk. Like the case-control study, this strategy is retrospective in approach. Schematically:



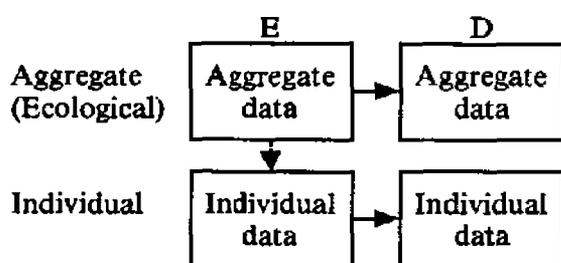
Unlike the cohort study, the cross-sectional investigation in and of itself pro-

vides no basis for ascertaining new disease events in E or \bar{E} subgroups and is therefore unable to provide certain knowledge about antecedent-consequent relationships. A similar deficiency regarding temporal sequence applies to case-control studies. However, the cross sectional study does allow inferences about absolute levels of disease frequency in the source population.

The strengths and weaknesses of these three study strategies will be amplified in the following sections. It should be noted here that descriptive or analytical studies can be conducted within the context of any one of the three basic study strategies.

Epidemiologic investigations can also be distinguished by the nature of the linkage between exposure and disease. Schematically, there are two types of exposure-disease linkages possible:

Type of Exposure-Disease Linkage



In individual risk studies, knowledge is gained of the exposure characteristics of diseased and disease-free individuals. In aggregate studies (as exemplified by investigations of geographical variations in disease distributions), the researcher obtains data *separately* on the frequency of exposure and disease in that place. No data are available on the exposure or other risk factor characteristics of individuals who actually died or survived; thus, there is no evidence that death or disease occurred in exposed individuals. Readers will commonly assume that such a link exists, but the fallacy of this assumption—the “ecological fallacy”—lies in the fact that individuals who died of the disease may not have been actually exposed to the study factor, even though they lived in a place characterized by a

high level of the exposure factor. For example, a small or large proportion of lung cancer deaths in counties having a petrochemical plant may be occurring in residents who had little or no occupational or environmental contact with the plant. Thus the aggregate study lacks linking evidence between exposure and disease at the level of an individual’s experience and, to this extent, cannot establish causal relationships or quantify the magnitude of a risk factor for disease. The aggregate approach is intrinsically incapable of providing evidence useful for testing hypotheses about risk factors for disease and should be conceptually limited to the descriptive or hypothesis-generating category.

In summary, epidemiologic studies can be categorized on several different dimensions relating to the study hypothesis, the temporal sequence of exposure-disease ascertainment, and linkage between exposure and disease. (See diagram below.)

DIMENSION	TYPE OF STUDY
Elaboration of the hypothesis regarding E and D association	Descriptive (hypothesis generating) Analytical (hypothesis testing)
Temporal sequence of exposure —disease ascertainment	Cohort Case control Cross sectional
Nature of linkage between E and D	Individual Aggregate (ecological)

Epidemiological Indices

Indices of Disease Frequency

Two conceptually distinct measures of disease frequency are employed in epidemiologic studies: *proportions* and *rates*. A proportion is a ratio in which the numerator is a component of the denominator, e.g., the proportion of workers employed in 1970 that have retired by 1980, the prevalence of byssinosis in a textile plant, or the number of cases of lung cancer developing over a 10-year period in asbestos workers employed in 1965. In each case, the numerator is a count of persons who have or develop an event of interest such as retirement, disease, or death. The denominator contains the count of persons in the numerator plus all other persons who were in the same study group at the time the counting began. The value of a proportion can only range from 0 to 1, and because the units are the same (i.e., persons) in the numerator and denominator, they cancel out and the proportion becomes a dimensionless quantity.

The two most common proportions used to measure disease frequency in epidemiologic studies are *cumulative incidence* and *prevalence*. *Cumulative incidence* (CI) is a relatively recent term introduced to distinguish between the incidence measure that is a true proportion, i.e., cumulative incidence, from the incidence measure that is a rate, i.e., incidence density (see below). CI is a simple proportion of the study population that develops new disease events (new cases of disease, disability, or death). In the framework of the 2 x 2 table given earlier

	E	\bar{E}	
D	a	b	m_1
\bar{D}	c	d	m_0
	n_1	n_0	N

the CI in the exposed population is:

$$CI_E = a/n_1$$

and the CI in the unexposed population is

$$CI_{\bar{E}} = b/n_0$$

In each case, n_1 and n_0 are a count of the number of exposed and unexposed persons at the beginning of the study. Thus, the cumulative incidence of lung cancer in a cohort of uranium workers, known to be alive and free of lung cancer in 1970, can be computed by following the cohort in time from 1970 to the termination of the study (e.g., 1980) and counting or accumulating all lung cancer cases developing in the cohort between 1970 and 1980. CI is meaningful only when the duration follow-up is given. *Prevalence* is also a proportional measurement, but it differs from cumulative incidence in that the numerator of a prevalence measure contains all diseased cases, whether new or old, that are "prevalent" at a point in time or during a time period. Thus a byssinosis prevalence of 0.20 signifies that 20% of the PAR was shown to have byssinosis, but no information is provided to determine whether the disease occurred recently or years ago. Prevalence is the measure of disease in cross-sectional studies.

Other epidemiologic indices that are propor-

tions representing disease frequency are *case fatality rates* (proportion of cases that are fatal), *cumulative mortality* (proportion of a PAR that dies, usually computed for specific causes of death), and *proportional mortality* (proportion of all deaths due to a specific cause). In case-control studies, no direct measures of disease frequency can be computed, since these studies begin with the selection of cases and controls without direct reference to an underlying PAR.

The second distinct measure of disease frequency is the disease or death *rate*, which is defined as a measure of change in disease incidence per unit change in person-years at risk (during a specified time interval). This measure of disease frequency is termed the *incidence density* (ID), and its units are cases (or deaths) per person-years (or population-time). Like CI, ID is meaningful only when the time period is stated, e.g., per year. The term "incidence density" provides a specific name for the disease measure that allows exits and entrances to the study cohort, by virtue of deaths or losses to follow-up or by hirings of new workers during the course of the study. Thus, some persons in the population at risk will have been "at risk" during the entire duration of a cohort study, while others will have died early or entered late, so that their "at risk" experience is shorter than the former group. In the frame work of the 2 x 2 table, incidence density is given as follows:

	E	\bar{E}	
D	a	b	m_1
Person-yr	N_1	N_0	

$ID_E = a/N_1$ $ID_{\bar{E}} = b/N_0$

N_1 and N_0 are not counts of exposed and unexposed persons but summations of the total time each member of the exposed and unexposed population remains in the study and free of disease, i.e., at risk.

A simple illustration will suffice to point out the difference between CI and ID. Assume that a cohort of 10,000 steelworkers is identified in 1970. Of these 10,000, 5,000 develop heart disease in the first year (an unrealistically high rate of disease). For ease of computation, assume that 1,250 cases occur on exactly each

terminal quarter of the year. Schematically, the PAR and deaths would be distributed as follows:

PAR	$\frac{t_0}{10000}$	$\frac{t_{1/4}}{8750}$	$\frac{t_{1/2}}{7500}$	$\frac{t_{3/4}}{6250}$	$\frac{t_1}{5000}$
Cumulative cases	0	1250	2500	3750	5000

$$CI = \frac{\# \text{ cases by } t_1}{\# \text{ PAR at } t_0} = \frac{5000 \text{ persons}}{10000 \text{ persons}} = 0.5 \text{ cases/person per year}$$

$$ID = \frac{\# \text{ cases by } t_1}{\# \text{ person-yrs. at risk}} = \frac{5000}{10000(0.25) + 8750(0.25) + 7500(0.25) + 6250(0.25)} = \frac{5000}{8125} = 0.61 \text{ cases/person-yr per year}$$

If all cases had occurred exactly on the first quarter date of the year the CI would be unchanged, but the ID would be:

$$ID = \frac{5000}{10000(.25) + 5000(.75)} = \frac{5000}{6250} = 0.8 \text{ cases per person-yr per yr}$$

If 6000 cases had occurred on the first quarter of the year, the ID would be

$$\frac{6000}{10000(.25) + 4000(.75)} = \frac{6000}{5500} = 1.09$$

cases per person-yr. per yr. while the CI would be 0.6 per year. Thus ID expresses the average rate of case incidence in the true population at risk and takes into account not only how many cases occur but the "speed" at which these cases develop. ID can range in value from zero to infinity; it does not represent the probability of developing disease, as CI does, but rather the force of morbidity or mortality in a population. Since the ID is computed for persons only when they are actually enrolled in the study, the ID measure allows exits and entrances to the study population between the start and ending of the study.

Measures of Effect

If a causal relationship exists between exposure and disease, the measure of this relationship is the measure of effect. In cohort studies, measures of effect can be relative or absolute. The *relative risk* (RR) is the common relative measure and is given by the ratio

$$I_E/I_{\bar{E}}$$

The absolute measure of effect is the *attributable risk* (AR)

$$I_E - I_{\bar{E}}$$

Since there are two types of incidence measures, we can distinguish two types of relative and attributable risk measures as well: the *cumulative incidence ratio* (CIR) and the *incidence density ratio* (IDR) as measures of relative risk, and the *cumulative incidence difference* (CID) and the *incidence density difference* (IDD) as measures of attributable risk. These values can be computed from the typical 2 x 2 tables.

	CI Study		
	E	\bar{E}	
D	a	b	m_1
\bar{D}	c	d	m_0
	n_1	n_0	

$$CIR = \frac{CI_E}{CI_{\bar{E}}} = \frac{a/n_1}{b/n_0}$$

$$CID = a/n_1 - b/n_0$$

ID Study

	E	\bar{E}
D	a	b
person-yrs.	N_1	N_0

$$IDR = \frac{ID_E}{ID_{\bar{E}}} = \frac{a/N_1}{b/N_0}$$

$$IDD = a/N_1 - a/N_0$$

In the cumulative-type study, n_1 and n_0 represent the PAR at the study's inception. In the density-type study, N_1 and N_0 represent person-yrs. of follow up.

CIR and IDR (the relative measures of effect) are better indices of the strength of a potential causal relationship between E and D; CID and IDD are better indices of the impact on public health associated with exposure or the potential benefit of a prevention program in absolute numbers.

In cross-sectional studies, the prevalence ratio (PrR) is the only measure of effect commonly reported, and, like the CIR, is given by the ratio $\frac{a/n_1}{b/n_0}$. However, in this approach, \underline{a} and \underline{b} represent prevalent exposed and nonexposed cases representatively.

In case-control studies, the measure of effect is the odds ratio (OR). The odds ratio is an estimate of the relative risk of disease, given exposure. In a typical 2 x 2 table, the data layout for a case-control study is as follows:

	E	\bar{E}	
D	a	b	
\bar{D}	c	d	
	a + c	b + d	

In a cohort study, the measure of effect for these data would be:

$$RR = \frac{I_E}{I_{\bar{E}}} = \frac{a/a+c}{b/b+d}$$

If the number of persons affected by disease is small relative to the number unaffected in the total population (the usual situation in studies of cause-specific diseases), then $a + c$ is approximately equal to \underline{c} , and $b + d$ is approximately equal to \underline{d} . Thus the estimate of relative risk

$$RR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

Thus $RR = OR = \frac{ad}{bc}$. The OR is a valid estimate of the relative risk derived from cohort studies provided two assumptions are met:

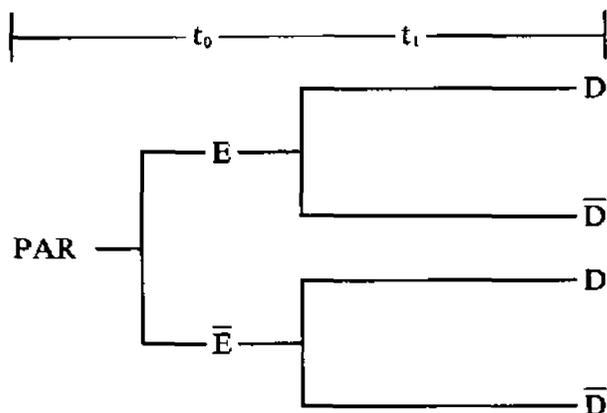
1. The disease is rare (thus $a + c$ and $b + d$ are reasonably approximated by \underline{c} and \underline{d} respec-

tively in the general population).

2. Cases and controls are selected independently of exposure status or of any factor associated with exposure.

C. COHORT STUDIES

Characteristics of Cohort studies



The essential features of a cohort study are:

1. The study factor (E) is characterized in each person at t_0 , prior to the appearance of disease.
2. The study population is observed (followed-up) longitudinally from t_0 to t_1 ; t_1 is determined by the onset time of disease or death, loss to follow-up, or cessation of the study.
3. New disease events occur between t_0 and t_1 .
4. Measures of disease frequency can be referred to the PAR.

Cohort studies can be retrospective (or historical) or prospective, depending on the temporal relationship between the actual starting date of the study and the time when new disease events occur.

1. A retrospective cohort study: t_0 and t_1 have already occurred when the study is actually initiated by the investigator. This is the most common form of cohort study in occupational epidemiology.
2. A prospective cohort study: t_1 has not occurred when the study begins, and data on the cohort is first collected in real time, t_0 . The study moves forward in real time, and new disease events are observed concurrently with the progress of the study.

Table I-44
LUNG CANCER IN COKE PLANT
WORKERS BY LENGTH AND
PLACE OF EMPLOYMENT

	Observed # Deaths	Observed/ Expected Deaths
Total coke plant	54	1.61*
5+ yrs in coke plant	46	2.09*
<5 yrs in coke plant	8	0.77
5+ yrs coke oven experience	40	3.67*
5+ yrs nonoven experience	5	0.51
5+ yrs oven topside	20	10.83*
5+ yrs oven side	18	2.49*

*p < .01

Source: Redmond et al. (23)

Examples

a. Retrospective cohort studies—Example: Long-term mortality study of steelworkers (12) (13)(23). In this series of studies, the mortality experience of nearly 60,000 steelworkers known to be alive and employed in 1953 in seven steel plants in Allegheny County, Pennsylvania, was followed retrospectively through 1966. Investigators determined the employment area of workers in 1953 from company employment records and compared the cause-specific observed mortality for a work area with expected mortality over the ensuing years, where “expected” was computed from the age and calendar year specific mortality of the total steelworker experience. Significant excess lung cancer mortality was reported for coke plant workers as shown in Table I-44. The observed/expected ratio was even greater among workers with five or more years employment in coke plants, with five or more years coke oven experience, and largest for workers with five or more years of

topside oven work experience. This stratification of lung cancer deaths by work area revealed the fact that the small excess of lung cancer in the total coke plant was accounted for by men employed at the coke ovens, but that in this group, a tenfold lung cancer excess appeared in workers on coke oven tops where greatest exposure to coal carbonization by-products would be expected. The investigators computed “expected” mortality by applying age, race, cause-specific mortality rates in the entire steelworkers cohort to age, race, cause-specific mortality rates in the subgroup of the population at risk, in a given work area, in each calendar year of follow-up. This effectively derived an incidence density measure (i.e., # observed deaths/# expected deaths for the person-yrs. at risk in each calendar year)—a conventional calculation in retrospective cohort mortality studies. The expected incidence density was based on a comparison population consisting of a working population in the same industry and in the same geographical region as the exposed group. This approach avoided many of the selection bias problems encountered when national mortality data are used as a source for comparison with the mortality experience of a working population.

In a later report, Redmond and Breslin compared observed cause-specific mortality for the total Allegheny County steelworkers cohort against expected mortality derived from age, race, calendar year, and cause-specific U.S. mortality rates and Allegheny County mortality rates (Table I-45) (22). The authors noted that if U.S. rates are used as a basis of comparison, one would conclude that lung cancer is significantly in excess in both white and nonwhite steelworkers, whereas if Allegheny County rates are used as the baseline, lung cancer frequency is about the same in steelworkers as in the county’s male population. It would, therefore, be erroneous to assume that the excess observed, when U.S. rates are applied, is directly related to occupational exposure. On the other hand, for many causes of deaths (such as cardiovascular and nonmalignant respiratory diseases) only overwhelming effects could be identified by using national or even regional data based on the general population’s mortality experience. This phenomenon of apparent selection, at time of employment, of persons at lower risk for many causes of death has been termed the “healthy worker effect” and is a form of selection bias

Table I-45

OBSERVED/EXPECTED MORTALITY RATIOS BASED UPON U.S. AND ALLEGHENY COUNTY RATES FOR ALLEGHENY COUNTY STEELWORKERS

Cause of Death	Whites		Nonwhites	
	Based on U.S. Rates	Based on Allegheny Co. Rates	Based on U.S. Rates	Based on Allegheny Co. Rates
All causes	0.83*	0.77*	0.73	0.68
Cancer of lung	1.28*	1.04	1.64*	1.03
Cardiovascular and renal diseases	0.80*	0.74*	0.64*	0.64
Nonmalignant respiratory disease	0.61*	0.63*	0.72*	0.58*

*p < .05

Source: Redmond and Breslin (22)

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that inadvertently occurs when the mortality experience of an occupational cohort is compared with that of the general population. The healthy worker effect appears to be greatest [cf. McMichael, (17)]:

1. at younger ages (less than 50-55 yrs.), when the selection process can better distinguish between the healthy and unhealthy.
2. for more overt disease manifestations such as cardiovascular and nonmalignant respiratory diseases, as opposed to cancer.
3. for nonwhites, whose employment opportunities often require better apparent physical health, or among whom a larger proportion of the general population may be in ill health relative to the employed.
4. for managerial, professional, business personnel, and department level supervisors than for clerical, semi-skilled operators, and unskilled workers.

b. Prospective cohort studies—Example: Lung cancer among uranium miners in the United States (1). Initial data for this investigation were provided from Public Health Service periodic medical surveys of uranium miners conducted during the period 1950 through 1960. Detailed occupational histories were obtained by personal interview at the time of each survey and were supplemented with annual uranium miner census information. Records were available for a

study group of 3,366 white and 780 nonwhite miners who had one or more months of underground uranium mining experience prior to January 1, 1964. The mortality experience of this group was followed from date of first examination through September 30, 1968. The investigation thus possesses elements of a prospective cohort study, since employment and initial health data were obtained simultaneously with the initiation of the study by the Public Health Service. However the mortality experience of the cohort was largely assessed retrospectively, after the 1968 termination date for the ensuing mortality analysis. Information on vital status was obtained from records of the Social Security Administration (a common source for such information in occupational mortality studies), from the Veterans Administration, and through the annual census of miners, mail questionnaires, post offices, obituary notices, employment agencies, credit bureaus, and inquiry of local residents and relatives. As a result of this intensive follow-up program, the vital status of more than 99% of the cohort was determined. Likewise, the cumulative exposure of the miners to radon daughters was assessed retrospectively from 43,000 measurements made for approximately 2,500 uranium mines between 1951 and 1968. Cumulative radon daughter exposure values were calculated for each miner from the date of his first hiring to each sequential month of observation until termination of employment, death, or the 1968 cut-off date. The observed/expected mortality for lung cancer among miners is given in Table I-46, where "expected" is com-

puted from age, race, calendar year, cause-specific mortality rates for the male population of the four-state area in which miners were examined (Arizona, Colorado, New Mexico, Utah). In this case, the comparison population is a general, regional population, and the healthy worker effect will influence the interpretation. The effect of radiation exposure on lung cancer risk appeared to increase with higher cumulative doses, though the effect at lower doses is difficult to evaluate because as workers aged, their cumulative doses increased and their person-years of exposure were shifted to the next higher cumulative exposure category. It is, therefore, unknown whether workers in lower exposure categories would have experienced greater lung cancer mortality than expected had they left the industry and not accumulated further occupational radiation exposures. The cohort was further stratified on years after start of underground mining and into miners with and without previous experience in nonuranium hard rock mines. In each case, cumulative radiation exposure was shown to significantly increase the risk of lung cancer.

The relative advantages and disadvantages of retrospective and prospective cohort mortality studies are listed in Table I-47.

Criteria for Evaluating Cohort Studies

Cohort studies are conceptually straight forward approaches to assessment of disease risk in exposed workers. The incidence of disease can be directly compared in exposed and unexposed groups. However, as in any observational study there are a number of pitfalls that can invalidate the results of a cohort investigation. The following aspects of design and conduct of an occupational cohort study should be evaluated:

1. Were the criteria for an individual's entry into the study cohort completely described? A cohort is a population group possessing some common linking characteristic, such as being employed in the same plant on a certain date or in a specified time period. Criteria for entry to a cohort can be: age range, years of hire, membership in a union, employment status in a plant, etc. A loosely defined cohort will make it difficult to evaluate exposure status and consequent potential for disease in the total

Table I-46

OBSERVED/EXPECTED LUNG CANCER DEATHS IN URANIUM MINERS ACCORDING TO CUMULATIVE RADON DAUGHTER DOSES

Estimated Cumulative Exposures (Working Level Months)	Person-yrs. at Risk	Observed/Expected Lung Cancer Deaths
≤120	8,516	0.55
120-359	9,355	4.67*
360-839	9,046	4.75*
840-1,799	6,607	4.76*
1,800-3,719	3,455	14.7*
3,720 +	<u>978</u>	<u>23.8*</u>
Total	37,957	5.98*

*p<.01

Source: Archer et al. (1)

cohort. In accumulating person-years at risk, it is important not to mix persons of varying risk status into the same analysis pool.

2. What are the potential effects of non-response or refusal to participate in prospective cohort studies? If nonresponse is disproportionate among subgroups of exposed persons who are at a greater risk of disease (e.g., among asbestos workers who are cigarette smokers), the true risk of occupational exposure can be seriously underestimated. A well-designed study should provide some information, if only on a probability sample, about characteristics of nonresponders.
3. Is the exposure status of the "exposed" cohort uniform or heterogeneous? In most occupational environments, some workers are more exposed to the study factor than others in the same plant. How well could the investigators stratify the cohort on exposure potential? Pooling a heterogeneous exposure group will dilute the true risk of highly exposed with the low risk of relatively unexposed members of the cohort.

Table I-47

RELATIVE ADVANTAGES AND DISADVANTAGES OF THE TWO TYPES OF COHORT MORTALITY STUDIES

	Retrospective Cohort Mortality Studies	Prospective Cohort Mortality Studies
<i>ADVANTAGES</i>	<ol style="list-style-type: none"> 1. Historical records are often available for complete enumeration of occupational cohorts. 2. Data are more readily accessible in a short time interval. 3. Lower cost. 4. An efficient, feasible means to evaluate carcinogenic risks in industry. 	<ol style="list-style-type: none"> 1. Investigators can predetermine the kind of data they wish to obtain. 2. Data collection can be subjected to quality control. 3. Information on important co-variables can be obtained. 4. Exposures can be directly measured, if necessary.
<i>DISADVANTAGES</i>	<ol style="list-style-type: none"> 1. Information on important extraneous risk factors is often lacking. 2. Exposures must often be assessed indirectly, from employment records. Direct (instrumental) measurements of exposure are often lacking. 3. Require relatively large sample sizes (thousands of person-yrs) for reasonable detection of disease risk. 	<ol style="list-style-type: none"> 1. High cost. 2. Time delay. 3. Often infeasible due to time or cost constraints. 4. Require relatively large sample sizes (thousands of person-yrs) for reasonable detection of disease risk.

4. How completely was the health or vital status of the cohort ascertained? Losses to follow-up greater than 10% subject a study to serious biases. A variety of standard techniques [cf. Boice (2)] are available to determine vital status, including searches of sources such as Social Security claims, vital registries of states, driver's license registrations, city and telephone directories, credit bureaus,

contacts with former neighbors or fellow workers, etc. Until the national death index becomes operational, no one information source is adequate for follow-up of mortality status in the United States.

5. How valid is the selection of the "exposed" or comparison cohort? Several biases, such as the healthy worker effect, are possible in selecting a reference population. The disease risk of the ex-

Table I-48

LEAST SIGNIFICANT RELATIVE RISKS FOR VARIOUS SAMPLE SIZES
IN A COHORT STUDY: TWO-SIDED SIGNIFICANT TESTS

Expected Annual Disease Rate in the Unexposed Group	Alpha Error	Person-yrs. of Follow-up per Exposure Group	Relative Risks at Beta Error of:	
			0.10	0.20
.01	.05	1,000	3.05	2.70
		10,000	1.51	1.44
		100,000	1.15	1.13
.01	.01	1,000	3.60	3.20
		10,000	1.62	1.54
		100,000	1.18	1.16
.001	.05	1,000	13.12	10.44
		10,000	3.07	2.70
		100,000	1.51	1.44
.0001	.05	1,000	>50	>50
		10,000	13.22	10.49
		100,000	3.07	2.71

Source: Walter (27)

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posed and unexposed cohorts should be equal, except for the fact of exposure. To achieve this equality, the two cohorts must be stratified on extraneous risk factors for disease. This stratification may be impossible if the comparison population is inherently less or more healthy than those possessing the study factor. Several reference populations are available for occupational cohort studies. These include samples of the Social Security Administration files; other work groups, e.g., comparison of asbestos and nonasbestos textile workers (cf. Enterline (8)); and comparison of subgroups with the total occupational cohort, e.g., coke oven workers with all steel workers (cf. Lloyd (12)).

6. Was the size of the cohort large enough to detect a reasonable relative risk, i.e., what was the "power" of the study? Schlesselman (25) and Walter (27) provide tables and formulae for computing the sample size necessary to detect the smallest relative risk that can achieve statistical significance, given predeter-

mined limits for alpha and beta errors and an expected frequency of disease in the unexposed population. As an example of the sample sizes required in cohort studies to detect various levels of significant relative risk, a portion of the calculations from Walter is reproduced in Table I-48 (27). The most important determinant of required sample sizes is the expected disease rate in the unexposed population. Studies of common diseases (such as cardiovascular disease) having an annual incidence rate of 0.01 could be designed with only 1,000 person-years of follow-up per group, to detect as significant a RR of 3.05. For cancer, specific sites in which the annual incidence might be 0.0001, 100,000 person-years of follow-up per group are required to detect a RR of 3.07. Note that these computations do not apply to study designs that utilize matching procedures and do not take into account stratification for various confounding factors.

Proportional Mortality Ratios

In some cases, all deaths occurring in a defined occupational cohort can be readily enumerated (e.g., through death claims against an employers' retirement system), but data are not as readily accessible on the size or composition of the population at risk. In these situations, neither cumulative incidence nor incidence density measures can be calculated. Instead, the relative frequencies of specific causes of death to total deaths (the proportional mortality ratio, or PMR) in the cohort can be compared with similar proportions computed for some comparison population such as the United States, the same state, or another occupational cohort. The PMRs can be adjusted for age differences in the 2 cohorts. Evidently, the sum of proportions for all causes will equal one in each group so that a relative excess for one cause in the study cohort will necessarily be offset by a deficit in other causes. The healthy worker effect and other problems affecting the validity of cohort studies will exist to the same degree in PMR studies. In addition, because of the offsetting problem already mentioned, it is likely that PMRs will suggest more deviations from the comparison population than will be detected by a true incidence study. Redmond and Breslin found 22 excesses or deficits in cause-specific proportional mortality of steelworkers by the PMR method, as opposed to 10 excesses or deficits detected by the standard cohort mortality study (22). The PMR method may be useful as a crude surveillance method, perhaps to suggest causes of death worth investigating in greater detail by the standard cohort or case-control study. However, the potential for false leads should be appreciated.

Standardized Mortality Ratio

The standardized mortality ratio (SMR) is the common summary measure of effect in occupational cohort mortality studies. This ratio is simply defined:

$$\text{SMR} = \frac{\text{Number of observed deaths in the exposed cohort}}{\text{Number of expected deaths in the exposed cohort}}$$

Where expected deaths are calculated by summing, overall ages, the product of the number of person-years for a specific age range in the study cohort and the cause-specific death rate

in the same age range of the comparison population. Thus:

$$\text{SMR} = \frac{\sum \text{observed deaths at age (i) in the exposed cohort}}{\sum \left(\frac{\text{person-yrs in exposed cohort at age (i)}}{\text{person-yrs in comparison cohort at age (i)}} \right) \left(\frac{\text{the death rate in the comparison cohort at age (i)}}{\text{the death rate in the comparison cohort at age (i)}} \right)}$$

The purpose of the SMR calculation is to obtain a summary estimate of the mortality experience of the study cohort relative to the mortality experience of a comparison cohort of the same age composition. The SMR standardizes for age distributions or for any other risk factor that the investigator wishes to standardize on, such as calendar year, smoking habits if known, etc. There is, however, one serious limitation, frequently overlooked, in interpreting the absolute magnitude of an SMR. This limitation prevents one from comparing one SMR with any other SMR and thus from concluding that an SMR of 150, for example, indicates a greater mortality risk than an SMR of 125 in another cohort. This incomparability of SMRs can be illustrated with the hypothetical data presented in Table I-49, where two occupational cohorts, A and B, have different age distributions but identical age specific death rates. The SMR for A and B is based upon mortality rates in the same comparison population. Since the age specific death rates of A and B are identical, we expect the age adjusted summary value for mortality risk (the SMR) in the two cohorts to be equal. They are not. Close inspection of the formula for computing the denominator of the SMRs shows why the inequality occurred. The SMR value is weighted by the size of the age specific population in each study cohort. In cohort A, a large proportion of the population was older, and this age group experienced twice the mortality rate of the younger group. Thus a relatively high "expected" value was obtained for the denominator. In cohort B, the opposite distribution of the population by age yielded a relatively low expected value, thus a high SMR. SMR (A) differs from SMR (B) because we have used different weights—consisting of the age specific population size actually found in each cohort—in calculating the "standardized" mortality ratio. In effect, the adjustment for age is *internal* to the age structure of each cohort and is incomparable to a second SMR computed for a cohort with a different age structure. Since SMRs are computed to standardize on age struc-

Table I-49
NONCOMPARABILITY OF SMRs

	Cohort A		Cohort B			Comparison Population		
	No. person yrs.	Death rate	No. deaths	No. person yrs.	Death rate	No. deaths	Death rate	No. person yrs.
Age 40-49	1,000	.022	2	5,000	.002	10	.001	3,000
Age 50-59	5,000	.004	20	1,000	.004	4	.003	4,000
Total	6,000		22	6,000		14		

$$SMR (A) = \frac{22}{1,000(.001) + 5,000(.003)} = \frac{22}{16} = 1.375$$

$$SMR (B) = \frac{14}{5,000(.001) + 1,000(.003)} = \frac{14}{8} = 1.750$$

$$SMR (A) \neq SMR (B)$$

Source: Author: Hypothetical Data.

ture, it is apparent they are inefficient in this respect and effectively useless in cases where age structures of two populations are different.

Miettinen has proposed an external weighting scheme for risk factor adjustment (e.g., age) that avoids the flaw in comparing SMRs (20). This externally adjusted measure of effect is termed the standardized risk ratio (SRR), and is given by:

$$SRR = \frac{\sum \text{expected deaths in the comparison population}}{\sum \text{observed deaths in the comparison population}}$$

$$= \frac{\sum \left(\frac{\text{size of the comparison population at age (i)}}{\text{population at age (i)}} \right) \left(\frac{\text{age specific death rate in the study cohort at age (i)}}{\text{age specific death rate in the comparison population at age (i)}} \right)}{\sum \left(\frac{\text{size of the comparison population at age (i)}}{\text{population at age (i)}} \right) \left(\frac{\text{age specific death rate in the comparison population at age (i)}}{\text{comparison population at age (i)}} \right)}$$

Computation of the SRR, using the same data as given previously in Table I-49, is illustrated in Table I-50. The SRR (A) is identical to the SRR (B), and it should be. The identity is achieved by using as weights the "external" age distribution of the comparison population. The same set of weights is used in computing the SRR for cohorts A and B.

The bias of the healthy worker effect will operate in SRR as well as in SMR calculations, if the comparison population is a mixture of workers and non-workers. However, SRRs can be compared from one occupational cohort to another as long as they are based on the same comparison population. In some cases, a sum-

mary measure of risk should not be derived at all, particularly when inspection of age specific death rates reveals very different values among two or more occupational groups. In these cases, the SRR (or SMR) will average out or at least obliterate these age specific differences and mask the true nature of the risk differences between the cohorts. If a prominent difference in age specific death rates is found for two or more cohorts, these age specific rates should be reported, otherwise important etiologic clues may be entirely obscured.

D. CROSS-SECTIONAL STUDIES

The conceptual starting point of a cross-sectional study is a population or a representative sample of a population, such as all workers in a cotton textile plant. Typically, this population is divided into exposure groups, where exposure is characterized on the basis of current job assignments, current environmental monitoring, or other risk factors observed in the population at the time of the study. Exposure groups are simultaneously assessed for the presence or absence of disease, physiological abnormalities, or other health outcomes of interest that are prevalent in the population at the time of the study. For example, the presence of symptoms characteristic of byssinosis or of lung function abnormalities in textile workers, subdivided into cotton dust exposure categories, illustrates the

Table I-50

SRR: EXTERNALLY ADJUSTED MORTALITY RATIOS

$$\text{SRR} = \frac{\text{expected deaths in comparison population}}{\text{observed deaths in comparison population}}$$

$$\text{SRR (A)} = \frac{3000(.002) + 4000(.004)}{3000(.001) + 4000(.003)} = \frac{22}{15} = 1.467$$

$$\text{SRR (B)} = \frac{3000(.002) + 4000(.004)}{3000(.001) + 4000(.003)} = \frac{22}{15} = 1.467$$

$$\text{SRR (A)} = \text{SRR (B)}$$

Source: Author: Hypothetical Data.

cross-sectional design. Although the prevalence of disease at the time of study can be referred to a defined population at risk, as in cohort studies, the cross-sectional approach provides no data on new disease events (incidence data) or on the rate of disease development over time. To this extent cross-sectional studies are plagued by two inherent limitations concerning temporal relationship between exposure and disease.

1. The *antecedent-consequent relationship* of exposure and disease cannot be determined because exposed and nonexposed groups were not selected prior to development of disease.
2. The study population available to the investigators may be unrepresentative of the original exposed and nonexposed populations due to selective survival or selective migration of workers because of health reasons. Particularly in occupational settings, it is entirely possible that workers severely affected by their work environment may leave, be transferred to other jobs, or otherwise selectively drop out of the high exposure situation. This form of selection bias is illustrated with hypothetical data in Table I-51.

To counter these problems, it is possible to account for past job exposures and job changes of affected and unaffected workers. Also, observations may be made on early retirees, workers who transfer from hazardous work environments and others who leave a particular job category. However, information on job history is difficult to obtain by questionnaire techniques, and personnel records of the present employer usually provide no useful data on work histories from other plants. Further, because cross-sectional studies often involve large study populations, a complex work history file on each subject may be a costly data acquisition and data management problem.

tional studies often involve large study populations, a complex work history file on each subject may be a costly data acquisition and data management problem.

The measure of disease frequency in a cross-sectional study is the prevalence (a proportion, not a rate) of affected persons in the population at risk. Prevalence is not a direct measure of disease risk in an exposed population because the nature of the study design does not generate incidence data. The prevalence of disease (or physiological abnormalities) in an exposed population is a function of two factors: the incidence and the duration of disease.

Prevalence = f (Incidence, Duration of Disease). A high prevalence may be brought about by a high incidence or by a long duration of disease. Cohorts enjoying better health care or favored treatment if illness develops may show a high prevalence of diseased workers, not because of high risk but due to longer "survival" of ill workers in the plant. Thus prevalence cannot be equated with incidence as a measure of disease frequency, and the prevalence ratio (PrR: ratio of disease prevalence in exposed to nonexposed) is not a wholly reliable estimate of risk associated with exposure. If however, incidence and duration are consistent over time or change equally in exposed and nonexposed groups, the PrR may be a valid indirect measure of relative risk (or cumulative incidence ratios). Unfortunately, there is seldom a basis for making these assumptions concerning change over time.

In many cases the nature of the occupational health problem is such that cross-sectional studies and generation of prevalence data are the only practical options available to an investigator. Such would be the situation where cumulative occupational exposures lead to increased risk of developing a chronic disease of insidious onset, such as chronic bronchitis or byssinosis. It is difficult to determine when these chronic respiratory diseases really begin and, for a retrospective cohort, to be certain who was free of the disease at some predetermined point in the past. Likewise, the cumulative exposure of working subgroups is usually difficult to evaluate. Ideally, one would like to begin with a standardized health examination that ascertains the presence or absence of chronic respiratory disease at the time of employment; follow different exposure groups serially with repeat health examinations; and finally assess the health status

of each exposure group at the study's termination. Unfortunately, such data are rarely generated, and selective losses of ill persons may still occur, although it would be possible to retrospectively evaluate the health status of the drop-outs and compare this with survivors in the same group.

Cross-sectional data are sometimes used to make geographical comparisons of disease prevalence between different countries, states, counties, or cities. These findings provide an index of the relative magnitude of a problem in different geographical areas and may be important in assessing the need for health care facilities and other resources. The prevalence of physiological abnormalities, such as impaired lung function or high blood leads, may provide the first clues to the existence of a work hazard. However, prevalence data should not be used to estimate disease risk unless there is reason to believe incidence and duration are relatively constant in exposed and nonexposed groups. Special efforts should be made to evaluate the possibility of selective survival or migration before drawing conclusions based on prevalence ratios.

Mortality Rates

Mortality rates have features of incidence and prevalence data in that the mortality rate in a given year is determined by the incidence, the duration or chronicity, and the virulence of the disease. For diseases such as lung cancer that are highly fatal in a relatively short time, mortality rates are reasonable indices of incidence rates. For avirulent diseases such as skin cancer, chronic musculoskeletal disorders, etc., mortality rates are totally unrepresentative of disease incidence. If persons survive for long periods with the disease—such as is the case with chronic respiratory or cardiovascular disease—mortality rates again do not reflect incidence unless survival (duration of disease) is relatively constant. Survival may be affected by temporal changes in medical care, by age at onset of disease, and by competing risks of death. Comparison of mortality rates in different geographical or occupational groups, when the mortality data were obtained outside the framework of a true cohort study, shares many of the limitations of prevalence data and should be interpreted similarly.

E. CASE-CONTROL STUDIES

Unlike cohort and cross-sectional studies, case-control studies are not inherently popula-

tion based, do not conceptually begin with exposed and unexposed groups, and provide no direct measures of disease frequency in a population. In spite of these negative aspects, the case-control study has become an efficient, powerful epidemiological tool that is finding increasing applications in etiologic research, particularly in the area of occupational and environmental cancer research. The case-control study may not seem to be a direct and logical approach to evaluating the risk of disease in exposed persons; however Cornfield (7) and Mantel and Haenszel (15) provided a theoretical basis for estimating relative risks from case-control data and the strength of this method is being increasingly appreciated.

A case-control study begins with the identification of all disease cases that can be found in a source population such as a hospital register, a state tumor registry, the insurance files of an employer, or in a population-based disease survey. Controls, defined as persons not known to have the disease, are selected from the same source population and are often matched to cases on basic demographic factors such as age, sex, and race. For efficiency, the size of the control group is usually equal to, or a small multiple of, the size of the case group. As a result, case-control studies typically have sample sizes of 200 to less than 1,000 subjects in total, whereas cohort and cross sectional study designs frequently involve many thousands of individuals or person years.

Analytical Aspects

The scheme for a case-control study is as follows:

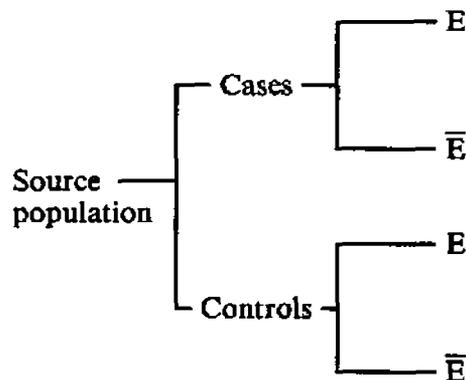
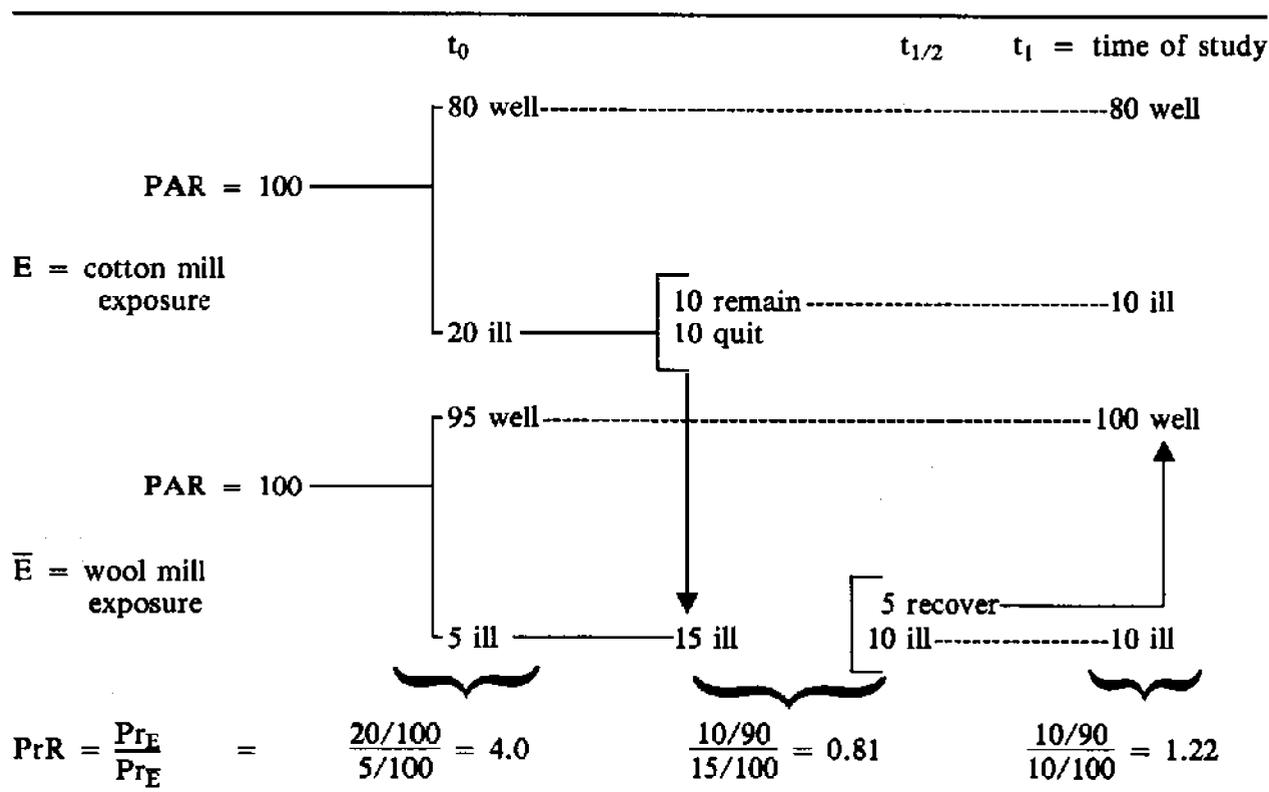


Table I-51

EFFECT OF SELECTIVE MIGRATION ON PREVALENCE RATIOS FOR RESPIRATORY DISEASE IN TEXTILE WORKERS



The initial (t_0) prevalence ratio (PrR) shows a fourfold greater prevalence of respiratory disease in cotton versus wool mill workers. Selective losses and migration of affected workers from cotton mills to wool mills results in a PrR of 0.81 at time $t_{1/2}$ (before the study actually begins). Recovery of ill persons due to cessation of exposure results in the PrR of 1.22 at t_1 , (the time when the cross-sectional survey is actually conducted). Source: Author: Hypothetical data.

	D	\bar{D}	
E	a	b	N_1
\bar{E}	c	d	N_2
	M_1	M_2	T

Exposure and other risk factor statuses of cases and controls are ascertained retrospectively. It is crucial to the study's validity that cases and controls be selected independently of exposure status. This independent selection can be a serious problem when cases are drawn from a source that is inherently at higher risk of disease (e.g., a hospital register) than the source for con-

trols (e.g., the general population). Unlike cohort studies in which N_1 and N_2 (in the above 2×2 table) are fixed (not random) at the start of the study, the number of cases, M_1 , and the number of controls, M_2 , are fixed while the outcome of interest is the exposure distribution among cases (a/M_1) and among controls (b/M_2). Having determined the cell frequencies a, b, c, d, in the 2×2 table, the odds ratio (OR) can be simply computed, as discussed in Section B, and is given by ad/bc . As demonstrated by Cornfield, the OR is a valid estimate of the relative risk of disease, given exposure (7). Mantel and Haenszel provide methods to compute the statistical significance of an OR or of an RR (15). For a case-control study, the significance of OR can be computed by applying the Mantel-

Haenszel X^2 test with one degree of freedom, where:

$$X^2_{MH(1)} = \frac{(N_1 + N_2 - 1)(ad - bc)^2}{N_1 N_2 M_1 M_2}$$

In case-control studies where each case and control is individually matched on a factor such as age, sex, and race, the 2 x 2 table takes a different form from that of nonpaired-matched studies. The exposure status of each case-control pair is considered and entered into the appropriate cell of a matched pair 2 x 2 table as follows:

Matched Pair 2 x 2 Table
Case-Control Study

		Controls	
		E	\bar{E}
Cases	E	r	s
	\bar{E}	t	u

In this table, r is a count of the pairs in which both the case and control are exposed, s is a count of the pairs in which cases are exposed and controls are unexposed, etc. In the matched pairs analysis,

$$OR = \frac{s}{t}$$

$$X^2 = \frac{(|t - s| - 1)^2}{t + s} \text{ (McNemar's Test)}$$

Design Aspects

In selecting cases, it is a distinct advantage to limit the case population to recently diagnosed or incident cases. Incident cases provide a more clearer differentiation between factors that influence disease etiology as opposed to those related to the duration and course of disease. Older cases still surviving are less representative of the population of cases in the source population. Incident cases offer greater potential for direct interviews or other means of acquiring fresh data concerning past exposures and other risk factor information.

It is desirable, though not essential to the

internal validity of a study, that cases and controls be representative of the source population at large from which cases were derived. For cases, the best way to assure representativeness is to include all cases that are known to have occurred in the source population within a defined time period. The following sources of cases have been utilized:

1. Hospital registers. Cole et al. enumerated all cases of bladder cancer reported in eastern Massachusetts hospitals during the 18 months ending June 30, 1968; obtained a probability sample of matched controls from the general population; and related the findings to employment in various industries (5).
2. State vital statistics registers. Brinton et al. identified, from state vital records, all cancers of the nasal cavity and sinuses occurring between 1956 and 1974 in North Carolina counties in which at least 1% of the population was employed in furniture and fixtures manufacture according to the 1963 U.S. Census of Manufacturers (3).
3. Occupational cohorts. McMichael et al. evaluated job titles of all cancer cases that were identified during the course of a retrospective cohort mortality study of four rubber plants (16). Cases occurred between 1964 and 1973.
4. Tumor registries. The National Cancer Institute has initiated a large case-control study of bladder cancer and saccharin use. Cases are being obtained from the 10 United States cancer registries that form part of the SEER Program (Surveillance, Epidemiology and End Results).

Each of the above sources of cases provides distinct advantages and disadvantages. Hospital registries generally are more accessible to researchers and allow easy validation of case reports against biopsy or autopsy evidence. However, a single hospital may not draw its patients from a clearly defined source population, and some cases of the disease from this population may go elsewhere, or not seek medical attention at all. Incident cases can most easily be identified through hospital registers. Vital records assure a nearly complete enumeration of cases, providing the disease is listed on the death cer-

tificate and sufficient time is allowed for nearly all diseased persons to have died. Hence, incident cases cannot be obtained from vital registries. Inaccuracies of diagnosis on death certificates must be assessed by linking death records to hospital records, a time consuming and logistically difficult procedure. Tumor registries, especially if state wide, offer nearly complete enumeration of incident cases, with reasonably good confirmation of diagnosis based on tissue samples. Unfortunately, there are very few comprehensive state-wide tumor registries in the United States. The hybrid design of a case-control study nested within an occupational cohort study is a recent method applied in studies of U.S. rubber workers [cf. McMichael (16)]. This approach affords a clear frame of reference to the source population from which absolute measures of disease risk can be derived. The design allows the investigators to assess how well controls are representative of the source population.

Selection of controls for case-control studies is a difficult epidemiologic issue. MacMahon cites several concerns in selection of controls (14):

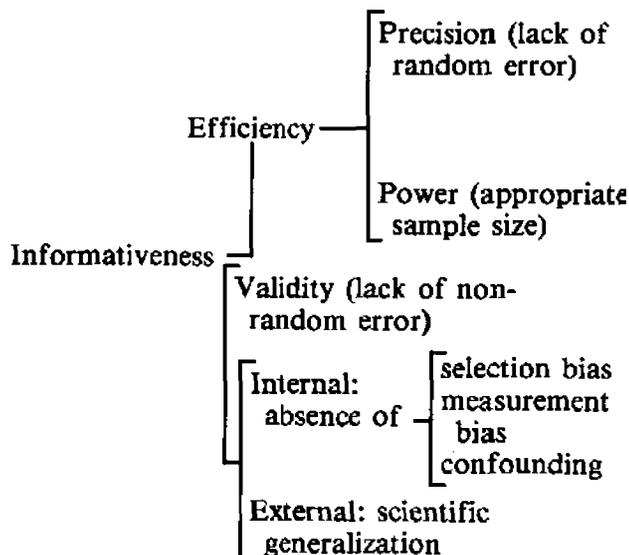
1. Controls should be representative of the source population at large from which cases were derived. The surest approach is to draw a probability sample of all noncases in the source population, but this is rarely feasible. Cole et al. obtained controls for their eastern Massachusetts bladder cancer study by having access to a published listing of all adult residents stratified by age and sex (5). Probability samples of the dead population of a state can also be obtained from vital registries. Controls drawn from the hybrid case-control-within-cohort design can also be obtained by probability sampling.
2. Information on exposure and other risk factors should be obtained with the same degree of accuracy and ease for both cases and controls. The problem is that cases may be so concerned that they (or their relatives) exhibit selective recall of past exposure or risk factor experiences. Live controls may provide better information on their own personal habits and employment histories than relatives of dead cases.
3. Controls should be similar to cases with respect to generally recognized, potentially confounding factors. Controls drawn from a different source population, e.g., hospital cases versus community controls, may differ in the distribution of other risk factors. These differences can be controlled by matching cases and controls in the selection process and a subsequent matched-pairs analysis or, after selection, by stratification analyses. Though there is considerable discussion in the literature on the advantages and disadvantages of matching in the selection process, most investigators agree that some form of stratification analysis is necessary to control for confounding [cf. Mantel and Haenszel (15)]. Matching during selection places constraints on what controls can be included and is perhaps most justifiable when it is very costly to obtain exposure and other risk factor information from cases and controls. Individual matching followed by matched-pairs analysis assures that cases and controls will be similar with respect to potential confounders that are the basis for matching. Thus, matching in the selection process assures that all cases and controls will provide useful information, while matching by stratification after analysis may cause some losses of unmatched cases or controls. Since it is seldom possible to match on all important potential confounders, matched pairs must often be disaggregated in order to perform a stratified analysis controlling for several confounders simultaneously. Over-matching in the design phase occurs when cases and controls are matched on variables that are not risk factors for disease or when subjects are matched on variables that are intermediate in the causal pathway (e.g., matching on lung function would minimize the likelihood of detecting a smoking effect). Similarly, if cases and controls are matched on county or city boundaries, their general environment (air and water quality) may be so similar that effects of certain aspects of environmental quality could not be detected.

In summary, the major advantages of case-control studies are: efficiency in terms of relatively small sample sizes required to detect minimum risks, ability to access and process more detailed information on individual exposure and other risk factors of interest, and a reasonable time frame for completion of studies.

The disadvantages are: risk of selection bias, difficulty of obtaining controls representative of the source population, difficulty of getting equally reliable information from cases and controls. The hybrid case-control within a cohort design is a promising method that overcomes some of these disadvantages and is particularly applicable for occupational studies of certain disease risks.

F. SOURCES OF ERROR IN EPIDEMIOLOGICAL STUDIES

Two major types of error in observational studies—random (sampling) and nonrandom (systematic) error—cause loss of information in epidemiologic data due respectively to loss of precision (efficiency) or loss of validity. The informativeness of a study may be considered as follows:



An informative epidemiologic study is one which can efficiently detect an association between exposure and disease, if the association truly exists, and which can provide a valid estimate of the association's magnitude.

Efficiency

Efficiency refers to concerns about random sampling, sample sizes, and statistical inferences from results obtained in the study population to conclusions about exposure-disease associations in the source population. Statistical *precision*, one component of efficiency, is a measure of the variability of repeated measurements of the same phenomenon, e.g., the incidence of lung cancer in the asbestos industry, or the prevalence of byssinosis in the textile industry. A better estimate of disease frequency will be obtained if some form of random sampling is used, and if the sample size is large enough to represent the source population, e.g., the plant or the industry. Thus, the precision of a study can be enhanced by increasing the sample size and obtaining better probability samples of the source population. Precision is inversely proportional to the variance of the estimate and thus to the confidence interval about the point estimate of the measure of effect, i.e., the relative risk, prevalence ratio, or odds ratio.

The power of a study refers to the adequacy of the sample size for detecting an effect, if one exists, at a certain minimum relative risk. If a tenfold disease excess in lung cancer exists among asbestos workers, a considerably smaller cohort can be studied than if a twofold excess were expected. A negative study may be accepted as an adequate assessment of exposure-disease relationships only if the sample size was large enough to detect a predetermined level of effect such as a twofold relative risk. If the sample size was sufficient only to detect a fourfold or fivefold relative risk, then a negative result may have little meaning.

Validity

Assuming that random or sampling error is reasonably controlled, a study can still yield an erroneous conclusion concerning the existence and magnitude of an association between exposure and disease in the source population. That is, the estimate of effect can be distorted by several systematic or nonrandom errors, and these errors are usually termed "biases." An example is the bias of the healthy worker effect, or of comparing hospital cases with community controls, or of confounding due to the mixture of exposure with another risk factor for disease. These errors are systematic in that they cause a

unidirectional deviation of the measure of effect toward or away from the null hypothesis of no effect.

The internal validity of a study refers to the agreement between an estimate of effect derived from a study sample and the level of effect that actually exists in the source population. Internal validity is distinct from statistical precision, and the distinction can be illustrated by an analogy. If 20 darts are thrown at a bull's eye, the spread and accuracy of the darts around the bull's eye may be characterized by one of four combinations:

		Spread = Precision (lack of random error)	
		P	P̄
On Target = Validity (lack of nonran- dom error)	V	VP	V̄P̄
	V̄	V̄P	V̄P̄

VP = all darts close together and on target (precise and valid)

V̄P̄ = darts are spread but center on the target (imprecise and valid)

V̄P = darts are close together but off target (precise and invalid)

V̄P̄ = darts are spread and center off target (imprecise and invalid)

Thus an odds ratio of 3.0 could be a valid estimate of the risk of leukemia associated with solvent exposure in dry cleaning plants, but, due to imprecision, the confidence interval about this point estimate could be so large as not to be statistically significant. On the other hand, an OR of 3.0 may be statistically significant but invalid due to confounding of solvent exposure with another risk factor for leukemia.

A second form of validity, external validity, refers to the ability to generalize as, for example, from the study of solvent exposure in a dry cleaning plant to solvent exposure under other circumstances (in other industries, other solvents, etc.). External validity is evaluated by a complexity of criteria that include considerations of consistency with other studies, biological plausibility, convergence of evidence from several biological disciplines, knowledge of pathophysiological mechanisms, evidence from experimental investigations, etc. Hence, while a

study may be internally valid, the ability to make scientific generalizations may be sharply limited by our lack of knowledge about the biological mechanism of the effect or the circumstances that may modify the association between exposure and effect. A single epidemiological study cannot be definitive on most of these issues, largely because of the complex nature of human responses to the total environment. External validity is a function of the breadth and depth of knowledge brought to bear on a subject by all biological disciplines, and it is within this context that questions of causality must be addressed.

Three sources of nonrandom error need to be considered in depth, since they are pervasive sources of bias in nearly all epidemiologic studies.

Selection Bias

Selection bias is a distortion in the estimated measure of effect due to the influence of the outcome variable (i.e., disease frequency in cohort studies, exposure frequency in case-control studies) on the selection of subjects into the study. For example, air pollution induced diseases may cause ill persons living in polluted areas to migrate to less polluted communities. Several forms of selection bias have been illustrated in previous sections:

1. The healthy worker effect: a selection bias that operates when mortality or morbidity of a working group is compared with that of the general population, components of which have poor health status.
2. Selective migration or survival: differential movement of persons affected by their exposures to less hazardous environments, such movement taking place prior to initiation of a study; survival of the healthier segment of a population exposed to an environmental hazard.
3. Selective losses to follow-up: disproportionate losses from a cohort of persons who are exposed and become ill.
4. The short-term worker effect: a phenomenon whereby short-term workers who move from one employer to another are often found to have below average health status and above average mortality. Failure to account for these workers biases

the estimated association between level of exposure (as indexed by duration of employment) and disease risk. Industries with high labor turnover are particularly subject to this bias.

5. **Case-control biases.** A number of subtle selection biases can operate to cause exposed cases to be more readily included in a study than exposed noncases. As an example, if cases of breast cancer were obtained from a screening clinic and controls from a community, a case-control study of birth control pills as a risk factor may be biased by the fact that pill users are more carefully watched for complications and therefore sent to breast cancer clinics. Similarly, hospitalized patients are, in general, more likely to be smokers and users of medications than community controls. The potential for selecting exposure-disease combinations needs to be carefully assessed when the results of any case-control study are interpreted. For a recent debate on this issue, refer to Horwitz and Feinstein (10) and a rebuttal by Hutchinson and Rothman (11). At times, an empirical approach may be taken to avoid selection bias in case-control studies, whereby dual controls are selected: one from the general source population (a "loose" control) and one from a population that is more closely matched to cases on potential confounders such as use of health care facilities, or date of hire (a "tight" control). Note: a more complete discussion of potential biases in case-control studies is given by Sackett (24).

Selection bias is more likely to be a problem in case-control and prevalence than in cohort studies. Cohort studies by definition begin with disease-free individuals, whether exposed or not. Of course, disease-prone individuals could have selected themselves out of the exposure cohort prior to the initiation of the study, but generally disease risk is not perceived differentially between exposed and unexposed groups.

To cope with selection bias, investigators can take several measures in the design and analysis phase of the study:

1. **In the study design:**
 - a. Reduce losses to follow-up in cohort studies by intensive follow-up efforts.
 - b. Reduce nonresponse rates or obtain information on a sample of nonrespondents.
 - c. Carefully select controls for cohort and case-control studies to assure that, under the null hypothesis of no effect, controls have the same risk as cases or that exposure status does not differentially influence the selection of cases and controls.
 - d. Make special efforts to obtain historical information on a sample of persons who departed from a plant or geographical area prior to the initiation of the study.
2. **In analysis:**
 - a. Try to estimate the direction of selection bias by analyzing data on a sample of nonrespondents or on "reluctant" versus "willing" responders.
 - b. Compare whatever is known about those lost, versus not lost, to follow-up.
 - c. Estimate the extreme situation for effect of losses to follow-up, namely that all losses from the exposed group remain disease-free, while losses from the nonexposed develop the disease.

Measurement Bias

Measurement bias is a distortion in the estimated measure of effect, due to errors in measuring exposure or disease status or to misclassification of subjects with respect to exposure or disease status.

Sources of measurement error include:

1. Variation among observers or instruments, or internal variation within the same observer or instrument: e.g., well trained radiologists may differently interpret the same chest roentgenogram.
2. Variation in the subject or exposure situation being measured, where our limited measurement systems fail to adequately represent these variations; e.g., one blood pressure reading is taken to represent an individual's blood pressure

status even though he may exhibit diurnal variations.

No instrument or observer can obtain perfect measurements at all times. Measurement bias refers to systematic, rather than random, errors associated with the taking of measurements. The epidemiologist uses two different but related terms to assess the presence of systematic error in measurements: *sensitivity* and *specificity*. Sensitivity is the proportion of true cases (or true exposures) detected as cases or exposed by a test, an observer, or an instrument. Specificity is the proportion of true noncases (or nonexposures) detected as noncases or nonexposed by a test, an observer, or an instrument. The concepts are well illustrated in a 2 x 2 table:

		Actual Disease (or) Exposure	
		D	\bar{D}
Test for presence of disease (or exposure)	D	a	b
	\bar{D}	c	d
		a + c	b + d

$$Se = \text{sensitivity} = a/a + b$$

$$Sp = \text{specificity} = d/b + d$$

Related to these measures are:

$$FN = \% \text{ false negatives} = c/a + b = 1 - \text{sensitivity}$$

$$FP = \% \text{ false positives} = b/b + d = 1 - \text{specificity}$$

Note that sensitivity provides information about persons with disease (or exposure), whereas specificity applies to persons free of disease (or to the nonexposed). In order to obtain estimates of sensitivity and specificity, it is necessary to obtain measurements of the same event (disease or exposure) by means of the usual test or instrument and by a second, more complete or accurate method that would be considered the standard of excellence. For example, one could test for chronic respiratory disease with ventilatory function and/or a form of the standardized chronic respiratory disease questionnaire. The same persons could then be carefully examined by a panel of experts who might perform a battery of diagnostic procedures, pool their findings, and attempt to reach diagnostic agreement. Similarly, an area monitor in a work place

might be compared with results from all individuals wearing personal monitors, combined with careful industrial hygiene evaluations, to assign an exposure value to a given job.

Although sensitivity and specificity measures are seldom obtained for most diagnostic and screening tests or for environmental monitors, users of these test instruments have the opportunity to develop their own validation procedures. The importance of sensitivity and specificity measures lies in the application of these measures to the assessment of measurement bias and the potential for obtaining corrected estimates of effect, once sensitivity and specificity are known. This use of sensitivity and specificity has not received the attention it deserves, and the importance of the point will be illustrated in the following:

1. Estimating the magnitude of information bias:

Assume that the following results are obtained from a cohort study:

		D		\bar{D}	
		a = 100	b = 400	c = 50	d = 450
E					$N_1 = 500$
\bar{E}					$N_2 = 500$
		$M_1 = 150$	$M_2 = 850$	$T = 1000$	

Cumulative Incidence Ratio (CIR)

$$= \frac{a/N_1}{c/N_2} = \frac{100/500}{50/500} = 2.0$$

Assume that the method for measuring exposure status can be shown to have a sensitivity of 90%, and a specificity of 90%, and that this measurement error is equal for diseased and nondiseased groups. Applying a 90% sensitivity (Se) and specificity (Sp) to the diseased and nondiseased groups separately, we obtain the following:

		Diseased		
		E	\bar{E}	
E	a' Se	c'(1 - Sp)	100 = a	
\bar{E}	a'(1 - Se)	c' Sp	50 = c	
		a'	c'	
		Se = 0.9	Sp = 0.9	$M_1 = 150$

Nondiseased
Actual exposure status

	E	\bar{E}	
E	b' Se	d'(1 - Sp)	400 = b
\bar{E}	b'(1 - Se)	d' Sp	400 = d
	b'	d'	
	Se = 0.9	Sp = 0.9	M ₂ = 850

The values a', b', c', and d', which are baseline marginals for the two 2 x 2 tables representing diseased and nondiseased subjects respectively, are the true exposure frequencies:

- a' = actual number of exposed diseased subjects
- b' = actual number of exposed non-diseased subjects

These values can be calculated, first by applying the known Se and Sp measures to the unknowns, a', b', c', and d', yielding the value given in the cells of the 2 x 2 tables immediately above.

It can be shown [cf. Shy et al. (26) and Copeland et al. (6)] that it is possible to solve for a', b', c', and d' in terms of Se, Sp, M₁, M₂, N₁, N₂, T, a, b, c, and d. Knowing the values of a', b', c', and d', we can calculate the true cumulative incidence ratio as follows:

For misclassification of exposure status

$$\text{True CIR} = \frac{a'/N_1}{c'/N_2} = \frac{(M_1 \text{ Sp} - c)(T\text{Se} - N_1)}{(M_1 \text{ Se} - a)(T\text{Sp} - N_2)}$$

Note: this formula applies to errors in measurement of exposure status.

An illustration from the above cohort study having Se = 0.9 and Sp = 0.9 is the following:

$$\text{True CIR} = \frac{150(.9) - 50}{150(.9) - 100} \frac{1000(.9) - 500}{1000(.9) - 500} = 2.43$$

The effect of equal misclassification of exposure status of diseased and nondiseased persons was to bias the RR estimate toward the null hypothesis of no effect, i.e., a bias from a true RR of 2.43 to an estimated RR of 2.0.

2. Estimating the direction of bias caused by measurement error:

a. Nondifferential measurement errors:

If diseased and nondiseased persons are equally misclassified with respect to exposure status (Se is same for D and \bar{D} and Sp is same for D and \bar{D}), the estimate of effect will always be biased toward the null hypothesis of no effect.

Illustration for cumulative incidence ratios, nondifferential errors follows:

Measurement Error:		Study Estimate		True CIR
Diseased	Nondiseased	of CIR		
Se	Sp	Se	Sp	
0.9	0.9	0.9	0.9	2.0
0.7	0.7	0.7	0.7	1.68
0.7	0.9	0.7	0.9	1.62
0.9	0.7	0.9	0.7	1.77

Note: Lower sensitivity produces a larger bias than lower specificity of the same magnitude.

b. Differential measurement errors: If diseased and nondiseased persons are unequally misclassified with respect to exposure status (Se and/or Sp are not the same for D and \bar{D}), the measure of effect can be biased toward or away from the null hypothesis.

An illustration for differential Measurement Error:

Measurement Error:		Study Estimate		True CIR
Diseased	Nondiseased	of CIR		
Se	Sp	Se	Sp	
0.9	0.9	0.9	0.7	1.38
0.7	0.9	0.9	0.7	0.82
0.9	0.7	0.9	0.9	2.56
0.9	0.7	0.7	0.9	3.51

Bias toward the null hypothesis occurs when:

- (1) measurement errors are greater among nondiseased persons who are truly nonexposed but classified as exposed (row 1)
- (2) measurement errors are greater among diseased persons who are truly exposed but classified as unexposed (row 2)

Bias is away from the null hypothesis when:

- (1) measurement errors are greater among diseased persons who are truly non-exposed but classified as exposed (row 3)
- (2) measurement errors are greater among nondiseased persons who are truly exposed but classified as nonexposed (row 4 which also includes low Sp for D group)

3. *Sensitivity and specificity applied to measurement of disease status:*

Observed cell frequencies in a cohort study

	D	\bar{D}	
E	a = 241	b = 2559	$N_1 = 2800$
\bar{E}	c = 158	d = 2042	$N_2 = 2200$
	$M_1 = 399$	$M_2 = 4601$	$T = 5000$

$$\text{Observed CIR} = \frac{241/2800}{158/2200} = 1.20$$

Assume nondifferential measurement errors in ascertainment of disease status:

$$Se = 0.866 \quad Sp = 0.974$$

$$\text{True CIR} = \frac{[a - N_1(1 - Sp)]/N_1}{[c - N_2(1 - Sp)]/N_2} \text{ For misclassification of disease status}$$

$$\text{True CIR} = \frac{[241 - 2800(1 - .974)]/2800}{[158 - 2200(1 - .974)]/2200} = 1.31$$

4. *To diminish information bias:*

- a. Improve questionnaires and measuring instruments.
- b. In data collection, pre-test questionnaires and train interviewers to be more objective and reproducible in their results.
- c. In analysis, obtain information on sensitivity and specificity of measurements, so as to allow calculation of the direction of bias due to measurement error.

Bias Due to Confounding

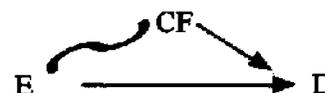
Confounding is a distortion in the estimated measure of effect due to mixing of the study fac-

tor effect (exposure) with extraneous risk factor effects. Confounding variables are likely to occur in most observational studies, simply because most diseases are not only multifactorial in etiology, but their virulence or impact on a population can be considerably modified or even ablated by a variety of circumstances. For example, the infectivity of tubercle bacilli is altered by the racial composition, nutritional and socioeconomic status, and age of the host population. Similarly, asbestos appears to be a far more effective carcinogen for smokers than nonsmokers.

To be a confounder, a factor must possess the following characteristics:

1. The confounder must be an *independent* risk factor or effect modifier of the disease. The confounder must not be an intervening variable or link in a causal chain, as would be the case for smoking-induced metaplastic changes in bronchial lining cells, where smoking is the true independent risk factor, metaplastic change is the intervening variable, and lung cancer is the end point in the causal chain. Knowledge of the existence of risk factors or effect modifiers must come from the body of literature on the disease of interest.
2. The confounder must simultaneously be correlated with the distribution of the exposure factor.
3. The association (correlation) between confounder and exposure must be demonstrated in the study population. The confounding attribute of any risk factor is not an inherent association of risk factors in the population at large but is merely a relationship that happens to occur in the population selected for study. For example, there is no inherent association between being an asbestos worker and a cigarette smoker.

The confounding relationship can be schematically represented as follows:



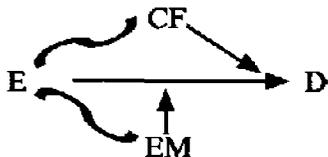
where the arrow indicates a causal relationship and the wavy line represents correlation but not

causality. The two essential features of a confounder are that it be an independent risk factor and that it be correlated in its distribution with exposure status.

Common examples of confounding factors that may be encountered in occupational health studies are:

1. Cigarette smoking as a potential confounder of the effect of occupational dust exposure or risk of chronic respiratory disease.
2. Alcohol habits as a potential confounder of the effect of exposure to an occupational liver carcinogen.
3. Dietary habits as a potential confounder of the effect of exposure to an assumed gastrointestinal carcinogen in the work or general environment.

Certain demographic characteristics of a population such as age, sex, and race are not biological "causes" of disease as such, but they alter or modify the apparent susceptibility of a population to disease. Many cancers and chronic degenerative diseases, such as emphysema and heart disease, are diseases of old age and are often more prevalent in males. Age and male-hood modify the risk for these diseases in the sense that a population of older persons is at greater disease risk than one of younger persons. These *effect modifiers* (EM) can become confounding factors when their distribution is disproportionate between exposed and nonexposed groups. The complete schematic representation of confounding shows that confounding can result from the presence of an extraneous risk factor (CF) or an effect modifier (EM), either of which is differentially distributed between exposed and unexposed study groups.



In this diagram the partial arrow from EM to the E→D association is meant to signify that the relationship is different at one level of EM (young age) than at another (old age).

Example of confounding: a positive association between E and CF

Assume a case-control study of the association between surface sources of drinking water and colon cancer.

(1) Simple analysis

	D	\bar{D}	
E	170	80	250
\bar{E}	80	170	250
	250	250	500

$$OR = \frac{170(170)}{80(80)} = 4.52$$

(2) Stratified analysis by urban vs. rural residence

Urban			
	D	\bar{D}	
E	150	30	180
\bar{E}	50	20	70
	200	50	250

$$OR = \frac{150(20)}{50(30)} = 2.0$$

Rural			
	D	\bar{D}	
E	20	50	70
\bar{E}	30	150	180
	50	200	250

$$OR = \frac{20(150)}{50(30)} = 2.0$$

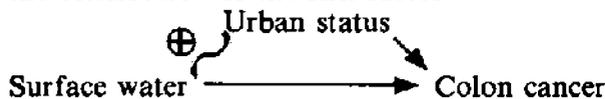
Note:

- (a) In the rural stratum, 70/250 subjects are exposed to surface water. In the urban stratum, 180/250 are exposed to surface water. Thus, urban status is correlated with exposure to surface water.
- (b) In the rural stratum, 50/250 subjects are

diseased. In the urban stratum, 200/250 subjects are diseased. The OR for disease, given urban vs. rural status is

$$\frac{200(200)}{50(50)} = 16$$

Thus urban status is a risk factor for disease. In this example, the measure of effect (the OR for surface water as a risk for colon cancer) in the simple analysis was confounded by urban status, which was both an independent risk factor for disease and was correlated with the distribution of the risk factor.



Example of confounding: a negative association between E and CF

Assume a cohort study of occupational dust exposure and chronic respiratory disease

	D	\bar{D}	
E	1,000	4,000	5,000
\bar{E}	1,000	4,000	5,000
			10,000

$$CIR = \frac{1,000/5,000}{1,000/5,000} = 1.0$$

(No apparent risk)

Stratify the population by smoking status

Nonsmokers

	D	\bar{D}	
E	350	3,650	4,000
\bar{E}	150	850	1,000

$$CIR = \frac{350/4,000}{150/1,000} = 0.58$$

Smokers

	D	\bar{D}	
E	650	350	1,000
\bar{E}	850	3,150	4,000

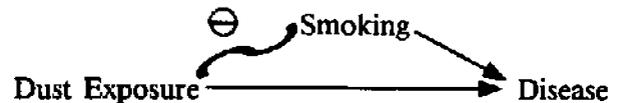
$$CIR = \frac{650/1,000}{850/4,000} = 3.06$$

Note that 4,000/5,000 nonsmokers are exposed to occupational dusts while 1,000/5,000 smokers are exposed.

Note also that smoking is a risk factor for disease (CIR = 3.0).

Thus, the true association of dust factor exposure with disease was confounded (in this case obliterated) by the negative correlation of smoking with dust exposure, when smoking itself was a risk factor for disease.

In this study, dust exposure had an effect on disease risk only in the presence of smoking. For smokers, dust exposure enhanced the risk of disease that was already increased by smoking alone.



The magnitude of the confounding effect can be simply quantified by the following equation (20):

$$RR_{CF} = \frac{RR_{Apparent}}{RR_{Standardized}}$$

where RR_{CF} is the relative risk (or other measures of effect) due to confounding, $RR_{Apparent}$ is the relative risk obtained when the confounding factor is not taken into account, and $RR_{Standardized}$ is the standardized relative risk measure obtained when the E→D relationship is adjusted for unequal distribution of the confounding factor between exposed and unexposed groups. $RR_{Standardized}$ can be obtained by computing SMR (or preferably an SRR) if age or some other single factor is responsible for con-

founding, or $RR_{\text{Standardized}}$ can be obtained by a stratified analysis that yields a summary estimate of overall effect adjusted for the distribution of several simultaneous confounding factors. Regression analysis or logistic risk functions can also be applied to an $RR_{\text{Standardized}}$.

Example

Assume a cohort study of 10,000 rubber workers followed for 10 years to evaluate the risk of benzidine exposure on bladder cancer incidence. Smoking is an independent risk factor for the disease and is correlated with the distribution of benzidine exposed workers.

		<u>Smokers</u>	
		D	Person-Yrs.
E	25	20,000	
\bar{E}	15	30,000	
		40	50,000

		<u>Nonsmokers</u>	
		D	Person-Yrs.
E	5	10,000	
\bar{E}	10	40,000	
		15	50,000

RR_A = Apparent RR due to benzidine

$$= \frac{\frac{25 + 5}{30,000}}{\frac{15 + 10}{70,000}} = 2.8$$

$RR_S = RR_{\text{Standardized}} = \text{SMR}$

$$= \frac{\text{Observed cases in exposed}}{\text{Expected cases in exposed}} =$$

$$\frac{25 + 5}{15/30,000(20,000) + 10/40,000(10,000)} = 2.4$$

$$RR_{CF} = \frac{RR_A}{RR_S} = \frac{2.8}{2.4} = 1.17$$

We can conclude that the true RR due to benzidine exposure is 2.4 and that the higher ap-

parent RR of 2.8 was due to the confounding effect of smoking which contributed 1.17 times the true RR to the apparent RR.

Methods for Controlling for Potential Confounders

Methods Used in the Selection of Subjects

1. Restricting of subjects to one category of the confounder or restricting eligibility into the study population for all subjects (e.g., only white males between the ages of 35 and 55 in 1960, or only nonsmokers).
2. Matching: restricting eligibility into the study population to subjects in the comparison groups (s) (e.g., pairing each case with one noncase of the same age, race, and sex). Matching along controls for confounding only in a cohort design. In a case-control design, matching must be coupled to a matched-pairs analysis to assure that confounding will be controlled.
 - a. Individual matching—selecting one or more comparison subjects for each index subject so as to be similar with respect to one or more variables.
 - b. Frequency matching—selecting a comparison group in such a way that it has the same distribution on one or more variables as does the index group.
3. Randomization—(in experiments) random allocation of “treatments” (i.e., the study factor) to the study population.
 - a. “Simple” randomization—no consideration of other factors in the random allocation of treatments.
 - b. “Restricted” randomization—consideration of other factors in the random allocation of treatments through blocking, grouping, and balancing.

Methods Used in the Analysis

1. *Stratification*—dividing the data into two or more extraneous variables, prior to further analysis (e.g., standardization). This is the main tool for ascertainment and control of confounding in epidemiologic analysis.
2. *Multivariate analysis*—using a statistical model to predict (or discriminate) the disease from two or more predictors, in-

cluding the study factor (e.g., multiple regression).

3. *Stochastic models*—fitting the data to a probabilistic model which assumes a particular configuration of factors, putatively involved in the etiology of a disease (e.g., Markov chain).

G. CRITERIA FOR INFERRING CAUSALITY

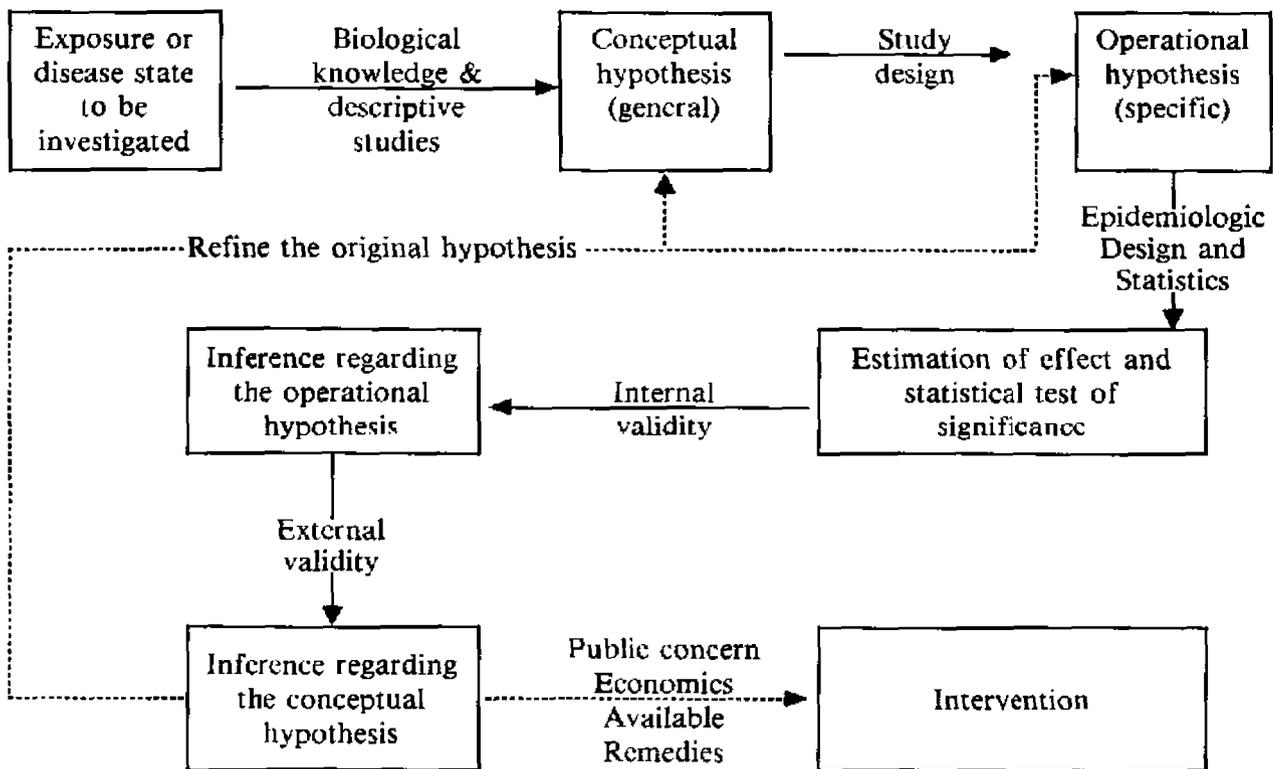
The process of inferring that an observed measure of effect (e.g., a relative risk of 2.5) implies causality entails answering three questions in sequence:

1. Is the effect (the relative risk of 2.5) a true effect in the sense that it is statistically significant, or is it merely a random observation, an extreme sample drawn from a population in which the true relative risk is 1.0? We answer the question by applying standard statistical methods with which we can measure the precision of our relative risk estimate.
2. Is the effect accounted for by something other than exposure, i.e., is the effect distorted by a systematic error, a bias due to selection, measurement errors, or confounding? To evaluate the possibility of bias, we must scrutinize the study design and the analysis and determine whether the investigators have avoided the various types of bias. We feel assured if the investigators use follow-up procedures for nonrespondents, measure sensitivity and specificity, and carefully examine the distribution of extraneous risk factors among exposed and unexposed groups. No study can be perfect in this regard, but we can attach a subjective weight to the evidence from each study as a function of the handling of potential biases.
3. Does the effect appear to be causal, i.e., is the exposure-disease association supported by evidence external to the study itself—by the total body of knowledge pertaining to the association between exposure and disease? Here we are referring to the external validity of the study, to the breadth of scientific generalization warranted by the addition of this study to the overall state of knowledge related to the study's conclusions. While formal

statistical tests guide us in answering the first question, and epidemiological principles of design and analysis are helpful in answering the second, there is no organized methodology so far developed for approaching this question. We are forced to rely on educated judgments that are necessarily subjective, even though these judgments may be based upon commonly accepted rules of scientific inference. In epidemiology, scientific inferences concerning causality cannot yet be based on immutable laws, mathematical or statistical computations, or entirely objective and repeatable experiments. Considerable judgment, based upon the experience and wisdom of the judges, must be brought to bear in deciding whether a body of evidence warrants the conclusion that a true causal relationship exists.

The judgmental process follows the general scheme of reasoning illustrated in Table I-52 for epidemiological investigations. Epidemiologists usually begin with the need to evaluate some public health problem: a disease whose etiology is not fully explained by known risk factors or an exposure that may be hazardous to public health. Descriptive studies may be carried out, to provide clues regarding high risk groups, environments associated with excess disease, or temporal patterns of disease variation. More importantly, the epidemiologist must turn to other biological disciplines and to previous epidemiological investigations, to assess whether there is a biological basis for postulating an exposure-disease relationship. To proceed without this basis is to run the risk of generating spurious associations without causal implications. The conceptual hypothesis that evolves from this reasoning is a general statement concerning an exposure-disease association—e.g., beryllium exposure is a risk factor for lung cancer. The conceptual hypothesis is not tied to any source population. To evaluate the conceptual hypothesis, it is necessary to design a study that can test the conceptual hypothesis within the specific time, place, and person circumstances of a source population in which some or all of the population members are exposed to the study factor. At this point, the study hypothesis becomes operational, with specifications related to the size and composition of the study popula-

Table I-52
A PROCESS FOR DRAWING CAUSAL INFERENCE FROM
EPIDEMIOLOGIC STUDIES



tion and the particular nature of its exposure, e.g., workers employed at a particular beryllium production process will show an excess relative risk of lung cancer when followed over the time period 1945-1975. It is now possible to choose an appropriate study design according to epidemiologic principles of good design; collect data; obtain measures of disease and exposure; estimate the effect; and apply tests to determine the statistical significance of the observed effect. The study now falls into the established framework of biostatistical analysis. Simultaneously, the study must be designed and analyzed to avoid the various forms of bias, and in interpreting their results, investigators need to consider whether other factors that could not be accounted for might have influenced the measure of effect. In most early studies, a careful scrutiny of results will reveal missing pieces of evidence, potential selection biases, inadequate measures of exposure, incomplete infor-

mation on disease status, or inadequate data on other risk factors. From this evaluation, investigators are able to refine and often restrict their conceptual hypothesis or to reformulate an operational hypothesis that is now enriched with considerably more specificity. Progress in epidemiology, as in all of science, is made by finding the exceptions to the rule, discarding old and developing new hypotheses that better explain present and previous observations. A skeptical attitude toward his own results forces the investigator to rethink his conclusions, challenge his assumptions, and design fresh studies that may considerably strengthen the basic conceptual hypothesis.

The process of hypothesis testing, refinement of knowledge and retesting of hypothesis has no clear demarcation between evidence of firm association and of causation. By the nature of observational studies on human disease risks, we know that an association may be greatly

altered by circumstances of person, place, and time. The magnitude of disease risk in one plant may be entirely different in another, even though the same product is manufactured in both. We remain skeptical about the applicability of conclusions from one study until we see the results replicated by other investigators in other population groups. Even the first studies of cigarette smoking and lung cancer were greeted with healthy skepticism by well established scientists.

At some point, however, the state of knowledge is such that it is possible to review the range of studies and question whether the evidence is sufficient to infer causality. Such questions are frequently asked by federal agencies responsible for developing occupational and environmental health standards for public health protection.

In 1965, Austin Bradford Hill addressed the question of association or causation in a paper that has become a classic for its clarity and wide acceptance (9). Hill presents a series of criteria that can be considered in judging whether evidence for an association warrants a causal interpretation. These criteria, listed in Table I-53, are not, in the author's words, "indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do... is to help us to make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more likely than cause and effect?"

All scientific evidence is incomplete, by the very nature of the hypothetical, deductive approach of the scientific method. A conclusion about causality may be upset or modified by advances in knowledge. However, it is unlikely a single study could contradict a body of evidence that meets the criteria of A. B. Hill. If a new hypothesis is advanced in competition with a well established conclusion, we should prefer the new hypothesis only if at least one of the following criteria is satisfied, as proposed by Buck in commenting on Karl Popper's philosophy of science (4):

1. The new hypothesis makes more precise predictions.
2. It explains more of the previous observations.
3. It explains the previous observations in more detail.
4. It has passed tests which the older hy-

pothesis has failed.

5. It has suggested new tests or made new predictions not made by the older hypothesis.
6. It has unified or connected phenomena not previously considered to be related.

Table I-53

**CRITERIA FOR INFERRING CAUSALITY
IN EPIDEMIOLOGICAL STUDIES**

-
1. Strength of the association (relative risk).
 2. Consistency: replication of results by different investigators in different places, circumstances, and times.
 3. Biological plausibility: depends on the current state of knowledge.
 4. Biological coherence: agreement of results with findings of experimental research and clinical observations (coherence of evidence among experimental and observational disciplines).
 5. Biological gradient: increase in disease with increase in intensity of exposure (dose-response curve).
 6. Temporality: exposure precedes disease.
 7. Specificity: the disease outcome is specific to, or characteristic of, exposure to a particular agent, e.g., pleural mesothelioma and asbestos (a weak criterion).
 8. Effect of intervention: removal of putative cause results in significant reduction in disease incidence.
 9. Analogy: drugs or chemicals that are structural analogues of a harmful agent may also induce similar harmful effects (a weak criterion).
-

Source: Hill, A. B. (9).

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Hence, confidence in making a causal inference should not depend on the lack of any alternative explanation, but on the ability to consider many alternatives, all of which can be rejected.

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RADIOLOGY

Russell H. Morgan

BASIC CONCEPTS IN RADIOLOGY

Historical Background

In 1895, when Roentgen discovered the x-ray, there followed a burst of scientific activity never before equaled. In medicine, the potential of this new form of radiation was recognized at once, and before the turn of the century, x-ray equipment was in active clinical use in every corner of the civilized world.

From these early times, the growth of medical radiology has been remarkable. The excitement that accompanied Roentgen's discovery has continued undiminished ever since. New techniques and methods employing x-rays have followed one another in rapid succession; today radiology finds itself at the center of clinical medicine.

The universal enthusiasm with which radiological methods have been accepted in medicine stems largely from the wealth of diagnostic information these methods provide. Nowhere is this more evident than in radiography of the chest where the information is of such fundamental importance that the chest radiograph has become an essential element in the clinical investigation of almost every patient and an epidemiological tool of great value in the study of dust-related occupational disease.

Properties of X-rays

In many respects, x-rays are similar to light. They travel in straight lines with a speed of 300,000 km per second. They blacken photographic film and cause certain crystalline materials to fluoresce. They tend to scatter when interacting with matter. They are composed of myriads of discrete bundles of energy, called photons. However, unlike light, whose photons contain only a small amount of energy (a few electron-volts), x-rays are very energetic (tens of thousands of electron-volts per photon). This difference causes x-rays to exhibit a number of

distinct properties.

X-rays have the ability to penetrate matter, the fraction of radiation either transmitted or absorbed by an object being dependent on (a) the object's density and thickness, (b) the object's elemental composition, and (c) the radiation's energy. This differential transmission and absorption of x-rays causes them, after passing through an object, to bear an image of the object's internal structure. Such an image can be converted to a visible image by means of an appropriate photographic film or fluorescent screen.

Radiation Hazards

In the beginning, the hazards of excessive x-ray exposure were not known. Although a few reports of x-ray "burns" began to appear in the medical literature as early as 1896, the first radiologists took few precautions to protect themselves from exposure to this new form of radiation. On the contrary, many of these pioneers fluoroscoped their hands each day to test their apparatus before their first patients were examined. It did not occur to them that such a practice might be unwise. Soon, the hands of these physicians became inflamed and underwent changes that often degenerated into skin cancer.

From these experiences, it was quickly realized that large exposures to ionizing radiation can be harmful and that radiologists should take measures to protect themselves from unnecessary exposure. Appropriate means were quickly developed and implemented and, for a while at least, the problems associated with excessive radiation exposure were resolved and concern for them faded.

A few decades later, Muller reported that even small doses of ionizing radiation produced

genetic aberrations within the progeny of irradiated species of fruit flies. Moreover, the changes seemed to be linearly related to radiation dose; were cumulative; and were not reversible (14).

Muller's work went largely unnoticed until shortly before World War II when scientists associated with American atomic energy research began to worry about the genetic effects of ionizing radiation received by large population groups. At the same time, interest in the somatic effects of ionizing radiation, including the development of malignant disease, was rekindled. Since then, studies of Japanese nuclear bombing survivors and of various clinical groups exposed during multiple x-ray procedures have added greatly to our knowledge of the small-dose effects of ionizing radiation.

In chest x-ray examinations, radiation hazards are fortunately small. With respect to possible genetic damage, the amount of radiation reaching the testes in men and the ovaries in women is vanishingly minute as long as examinations are carried out with the x-ray beam limited to the thorax (chest) by collimation. Collimation is widely used in practice today and is a requirement of all NIOSH providers.

With respect to possible somatic damage, chest x-ray examinations deliver relatively small doses of ionizing radiation to the thorax due to the low density of the air-containing pulmonary tissues. As a consequence, approximately 20 posteroanterior radiographs of the chest may be performed on an individual in a given year, with the delivery of a mean radiation dose to the intrathoracic tissues no greater than that received annually from natural background sources at sea level. Although unnecessary radiation is something to be avoided at all times, present knowledge indicates that radiological examinations of the chest, judiciously planned and executed, do not constitute a significant hazard to health.

TECHNICAL ASPECTS OF RADIOGRAPHY

The Formation of Radiographic Images *X-ray Production*

X-rays are produced whenever electrons impinge on matter at high velocity. To take advantage of this phenomenon, an x-ray tube consists of an evacuated glass envelope in which are mounted a source of electrons and a metallic

target on which the electrons can be projected. Conventionally, the electron source is a filamentary wire which, when electrically heated to incandescence, emits electrons into the surrounding vacuum. These electrons are attracted to the target and x-rays are generated when a high electrical potential (several kilovolts), positive in polarity, is applied to the target.

In radiography of the chest, x-ray tubes must be operated at very high capacity. This is to assure that exposure times will be sufficiently short (e.g., 1/60 sec.) to avoid blurring of the radiographic images from heart motion. This requirement creates serious problems for the x-ray design engineer because x-ray production is a relatively inefficient process. Only a small fraction of the electronic energy developed in an x-ray tube is converted to x-radiation. The remaining energy is converted to heat, and when a tube is operated at high capacity, means of dissipating this heat must be provided before damage to the tube occurs. The problem is made particularly difficult by the fact that the tube's electrons must be focused on a very small area of the target (e.g., 1.5 mm sq. or less) if the radiographic images of all structures, both moving and stationary, are to be clear and sharp.

Because of these considerations, the targets of today's x-ray tubes are made of tungsten, a metal that is not only a relatively efficient x-ray emitter but a metal that has a high melting point. Moreover, the tungsten is arranged in the form of a disc which rotates in front of the electron source in a manner such that electrons fall successively on different areas of the disc during x-ray emission. Heat is thereby distributed over a large area of the target while x-ray emission appears to occur from a fixed locus. By these provisions, x-ray tubes with small focal spots can be operated at high capacity to yield x-ray images of excellent quality even in the presence of vigorous heart motion.

X-rays are emitted in all directions when electrons impinge on the target of an x-ray tube. For this reason, it is necessary to encase such tubes in leaded enclosures which prevent the escape of radiation except that coming through a small opening in the enclosure located close to the tube's target. This emerging radiation is further restricted by appropriate collimating devices—external to the tube—that prevent anatomical structures, other than those under exami-

nation, being irradiated. Moreover, aluminum filters, 2 mm to 3 mm in thickness, and placed directly in the emerging x-ray beam, remove components of the radiation which do not contribute significantly to the formation of x-ray images but which otherwise would add to the radiation dose received by the subject under examination.

Image Formation

Although x-rays have the ability to penetrate matter, only a fraction of the radiation falling on an object emerges from the opposite side. The remaining radiation is either absorbed in or scattered by the object. The fractions of radiation transmitted, absorbed, or scattered by an object (such as an anatomical structure) depend on the density and thickness of the structure its elemental composition, and the energy of the photons comprising the x-ray beam. Consequently, the x-rays transmitted by an object bear an image of the object's internal components.

For example, when x-rays are projected through a person's chest, the amount transmitted in the regions of the lungs is relatively large, because only small fractions of the incident radiation are absorbed or scattered by the air-containing pulmonary tissues. On the other hand, the amount of radiation transmitted in the region of the heart is relatively small, because the heart and its contents are quite dense. The radiation transmitted by the ribs is smaller still, because ribs contain calcium salts which absorb incident radiation to a much greater degree than the surrounding tissues, despite their short path length.

If the radiation transmitted by the chest falls on a photographic film, a visible image is created when the film is processed, with the areas of the film under the lungs being relatively dark and the area under the heart much lighter. Images of ribs superimposed upon the lung fields and heart are comparatively lighter still.

In addition to gross outlines of the lungs, heart, and ribs, fine detail within these structures can also be recorded if the x-ray tube has a small target area from which x-rays are emitted (i.e., a small focal spot); is operated with a short exposure time; and is placed a long distance (e.g., six feet) from the patient and film. Under these circumstances, images of the lungs' branching blood vessels can be recorded, appearing as relatively light structural patterns against the

dark background of the air-filled pulmonary tissues.

No images of the peripheral bronchi or of their branches are seen under normal circumstances. Because these structures are air-containing, they transmit the same amount of x-rays as the lungs' air sacs; hence, no images of them are produced. However, if the air sacs contain fluid (as in pneumonia), and consequently become dense, the air-containing bronchi then create images that stand out in sharp contrast to those of the surrounding air-filled lung.

Recording Media

Photographic films, including those developed specifically for the recording of x-ray images, absorb very little of the x-radiation projected on them (about 2%). Consequently, large amounts of radiation are needed to produce satisfactory radiographic images unless some means is provided to make greater use of the available x-ray energy. Intensifying screens constitute just such a means. They are thin, yet rigid, sheets of radiolucent material, the size of an x-ray film, which are coated with a thin layer of fluorescent material composed of heavy-element crystalline salts whose x-ray absorption is relatively high (30% or more).

X-ray film, unlike conventional photographic film, is coated on both sides. Intensifying screens are normally produced in pairs, with one screen placed in apposition to the front surface of an x-ray film and the other in apposition to the film's rear surface. This duplication of screens increases the efficiency of x-ray capture. When exposed to x-rays, the intensifying screens fluoresce, converting the absorbed x-rays to light. The light then exposes the film.

A wide variety of films and intensifying screens are available to the radiologist. These range in sensitivity or speed from very slow, which require the delivery of a relatively large radiation dose to a patient, to very fast, requiring the delivery of a relatively small dose. In general, a film-screen combination's resolution (i.e., ability to record fine detail) varies inversely with its sensitivity or speed. In chest radiography, particularly when pneumoconiosis is a possible diagnosis, it is usually advisable to employ medium-speed films and screens. Such a combination should record the images of small pneumoconiotic lesions with sufficient detail to assure their easy recognition and yet not cause the de-

Table I-54

**REPRESENTATIVE FILM-SCREEN COMBINATIONS OF THE MID-SPEED CLASS,
SUITABLE FOR RADIOGRAPHY OF THE CHEST**

Film	Screens	Rel. Speed#	QMI*
Class A	DuPont Par Speed	0.40	2.8
Class A	G.E. Blue Max I	1.00	4.2
Class A	Kodak X-Omatic Reg.	0.80	4.2
Class A	USR Rarex BG Detail	0.50	2.7
Class B	DuPont Par Speed	0.80	3.9
Class B	G.E. Blue Max I	2.00	6.0
Class B	Kodak X-Omatic Reg.	1.60	4.6
Class B	USR Rarex BG Detail	1.00	3.8
Class C	Kodak Lanex Fine	1.00	5.5
Class C	3M Alpha-4	1.50	4.9
Class D	Kodak Lanex Fine	1.30	6.3
Class D	3M Alpha-4	2.00	5.7

*Quantum Mottle Index, a measure of film granularity due to the discreet nature of x-ray photons.

Class A Films:—DuPont Cronex 7, Kodak XG

Class B Films:—DuPont Cronex 4, DuPont Cronex 6+, Kodak XRP and 3M, Type R

Class C Film:—Kodak Ortho G

Class D Film:—3M, Type XD

#Measured as the reciprocal of the radiation exposure in milliroentgens required to produce an optical density of 1.0 in the processed film.

livery of large radiation doses to patients.

Table I-54 lists a number of film-screen combinations of the mid-speed class that are suitable for chest radiography (15). Many physicians and technologists prefer combinations using class A and class B films because of the greater number from which to choose. Moreover, these films are sensitive only to blue light, in contrast to the green-sensitive class C and D films. Darkroom fogging tends to be encountered less frequently with such films.

Table I-55 lists the gradient and latitude characteristics of the films included in Table I-54. The gradient of a film is a measure of its contrast-recording ability. Latitude is a measure of the extent to which technical errors of exposure may be made without causing deterioration of image quality. These two parameters vary inversely with one another, i.e., films with high gradients generally exhibit less latitude than those with low gradients and vice versa.

Table I-56 lists resolution and absorption characteristics of the intensifying screens included in Table I-54. Resolution is a measure of a screen's ability to record detail; absorption a

**Table I-55
CHARACTERISTICS OF
REPRESENTATIVE FILMS OF
THE MID-SPEED CLASS**

Film	Gradient	Latitude
DuPont Cronex 4	3.0	0.58
DuPont Cronex 6+	2.6	0.67
DuPont Cronex 7	3.0	0.58
Kodak XG	3.0	0.58
Kodak XRP	2.8	0.62
Kodak Ortho G*	2.4	0.73
3M Type R	2.4	0.73
#M Type XD*	2.9	0.50

*Green sensitive, for use with green emitting screens.

measure of the amount of radiation available for image production. It is wise to use screens with a high percentage absorption, so long as resolution is not sacrificed, because the radiation dose delivered to a subject during radiography is inversely related to the amount of radiation absorbed by the intensifying screens.

Generally speaking, it is desirable to use

Table I-56
CHARACTERISTICS OF
REPRESENTATIVE INTENSIFYING
SCREENS OF THE MID-SPEED CLASS

Screens	Rel. Resolution	% Absorption
DuPont Par Speed	1.4	21
GE Blue Max I*	1.5	32
Kodak Lanex Fine* +	2.1	34
Kodak X-Omatic Reg.	1.5	37
3M Alpha-4* +	1.7	42
USR Rarex BG Detail*	1.4	34

*Rare earth screens; + green emitting screens.

**These values apply to conditions in which an 80 kVp x-ray filtered with 3.5 cm Al, is used.

film-screen combinations with relative speeds ranging from 1.0 to 2.0, with quantum mottle indices of 5.0 or less and with screen absorption values of 30% or more. Under these conditions, the clarity of recorded images should be excellent and subject exposure small.

Image Quality

Image quality is the attribute of a radiographic film denoting the clarity with which recorded images are perceived, and hence, is as much an attribute of the observer as of the roentgenogram. Image quality is governed by a large number of factors, including characteristics of the structure under examination, a number of physical factors associated with the exposure, processing and visualization of the radiographic film, and the educational background and psychological state of the observer. Although many of these factors can be measured objectively, image quality is a parameter amenable only to subjective measurement due to the psychological element involved in its evaluation. Hence, the image quality of a particular radiograph may be perceived quite differently from one observer to another. This obviously creates problems for the technologist who serves a group of physicians, or who makes films that may be reviewed by a number of observers. Frequently, a film is judged acceptable by one physician, only to be rejected as unreadable by another. Image quality appears to bear a strong, inverse relationship to the interpretive difficulty a physician experiences with pathological changes recorded in a film. Often, films of excellent quality on purely technical grounds are rejected as "unreadable" when they contain patterns difficult to evaluate clinically.

cally.

So image quality is a parameter of enormous complexity. The more important aspects of the way radiographic technique can be used to enhance the quality of images seen in chest radiography follow:

Image Detail and Contrast

Two of the principal factors controlling image quality are the detail and contrast with which images are recorded. For purposes of this discussion, image detail is defined as the minimum limit of image size perceptible in a film. For radiographic films made with medium-speed intensifying screens, this limit is a diameter of 0.1 to 0.2 mm *when the images are of high contrast*, and when films are made under ideal technical conditions. Image detail is considerably poorer when images are blurred by movement of anatomical structures under examination, or by the use of an x-ray tube whose focal spot is excessively large. Image blurring and degradation also occur if the intensifying screens of a film-screen combination are not in uniformly firm contact with the film.

Image detail is also affected by image contrast, decreasing as contrast diminishes. In radiography, it is convenient to recognize two types of contrast: specific and gross. Specific image contrast is the difference between the blackness or optical density of the image of a given anatomical structure (or lesion) and the blackness or optical density of the immediate surrounding field. Gross image contrast, on the other hand, is the difference between the blackness or optical density of the darkest image of diagnostic interest in a film and the blackness or optical density of the lightest image of diagnostic interest.

Parenthetically, optical density is a quantitative measure of a film's blackness. Specifically, optical density at a given point in a film is the negative logarithm of the film's fractional light transmission. For example, a film which transmits one-tenth of the light incident on it has an optical density of 1.0; a film which transmits one-hundredth of the light has an optical density of 2.0.

Radiographic Exposure and Film Density

A radiographic film's blackness or optical density is a function of the x-ray exposure received by the film, rising from a value of zero, when no exposure is given, to values in excess of 3.0, when exposures are large (see Figure

I-15). This entire range of blackness or optical density, however, is not useful for clinical radiographic purposes. For example, if film receives an exposure (with characteristics shown in Figure I-15) of 1 mR directly under a subject's pneumoconiotic lesion, and the exposure received by the film from the region immediately adjacent to the lesion is 25% greater or 1.25 mR, the contrast between the lesion's recorded image and its surrounding field will be 0.3 units of optical density (Figure I-16). If the film under the lesion receives an exposure of 0.4 mR, the surrounding field receives 25% more or 0.5 mR. The contrast of the lesion's image under these circumstances will only be 0.15 units of optical density, due to the shallowness of the film's density vs log exposure curve at low exposure levels (Figure I-17). This loss of contrast is detrimental to image clarity and should be avoided. In practice, image contrast is usually judged unacceptable when a film's optical density is less than 0.2.

If the film under the lesion receives an exposure of 2.5 mR and the surrounding area 25% more or 3.125 mR, the image contrast will now be 0.275 units of optical density or closely the same as that when the exposure was 1 mR (Figure I-17). Under these circumstances, one might assume image clarity to be good. Such, however, is not the case under conventional viewing conditions. As images become darker, an observer's contrast discrimination diminishes noticeably. Moreover, even though the image contrast recorded by a film is good when the film's optical density is 1.7 or 1.8 and greater, the radiographic images are so dark that ambient light in the viewing room entering the observer's eyes and diffused by particulate material in the eyes, fogs the visual images and reduces their contrast to unacceptable levels. Ambient light in the viewing area should be maintained as low as possible. Otherwise, image contrast at the retina may fall to unacceptable levels at optical densities well below 1.8.

Useful Range of Optical Density

The useful range of film blackness for radiographic purposes extends from an optical density of about 0.2 at its lower limit to a density of 1.8 at its upper limit.* Such a range would be adequate for all radiographic purposes if, in practice, physicians were interested only in seeing images of simple anatomical structures,

recorded one at a time. Under these circumstances, technologists would merely expose film to a point where a desired image produced (in the processed film) a density somewhere in the middle of the useful range and a good film would *a priori* be produced.

However, the chest is not a simple structure. It is extremely complex, and its radiographic images must be recorded all at once. Moreover, these images produce optical densities within the film that extend through wide limits. Hence, depending on what structures a physician wishes to see, a film's useful density range is often more than filled. For example, some physicians feel it would be desirable if, on a single film, one could record with excellent detail and contrast the images of the peripheral lung fields, the hilar blood vessels and lymph nodes, the heart and other mediastinal tissues, all of the osseous structures of the thorax and more. Unfortunately, this ideal cannot be reached because it is impossible to crowd images of all of these structures into the limited range of optical density available, and still retain levels of image contrast sufficiently high to permit these images to be seen well. Physicians must be satisfied with much less, and most find it acceptable if only images of the lung fields and hilar regions are included within the useful range of film density.

Because image contrast and clarity are closely related, it is generally important that as much of a film's useful range of optical density as possible be filled by images of diagnostic interest. Under these circumstances, both specific and gross image contrast levels approach their maxima. However, when the useful range is fully occupied, the technologist is left with little latitude in estimating the proper exposures to be given when radiographic films are made. Small errors of over- or underexposure will yield unacceptable films. Therefore, it is usually wise to limit gross image contrast to a level moderately below its maximum (i.e., moderately less than 1.6 units of optical density). Figure I-18 illustrates the amount of latitude available to the technologist when the gross image contrast is 1.2 units of optical density. Even under these conditions, the technologist has relatively little latitude for error.

*Useful information is also recorded above a density of 1.8 and can be recovered with the use of a high intensity illuminator. However, this procedure is impractical when dealing with large numbers of films as in the interpretation of pneumoconiosis radiographs.

Scattered Radiation Effects

Under some circumstances, optical densities of images of diagnostic interest fall far short of filling the useful range of film density, due to the presence of one or more factors impairing image contrast. The most serious of these is scattered radiation which, when excessive, fogs the film and sharply impairs image quality.

Scattered radiation increases rapidly as patient size and thickness increase. To a lesser extent, scattered radiation levels become greater when the electrical potential (kilovoltage) of the x-ray tube is raised.

The amount of scattered radiation reaching a radiographic film can usually be reduced to acceptable levels by the use of a grid—a device composed of alternating sections of radiolucent and radiopaque materials—which attenuates the scattered radiation while allowing image-bearing x-rays to pass through. Scattered radiation can also be reduced by increasing the distance be-

tween patient and film, but this can cause loss of image detail and a disproportionate increase in the radiation exposure of the patient.

High Kilovoltage Techniques

In recent years, the electrical potentials or kilovoltages applied to x-ray tubes during chest radiography have been raised substantially to improve the image quality of pulmonary and other nonosseous structures. By the use of potentials of 300 kVp and more, in contrast to conventional voltages of 80 to 125 kVp, x-ray absorption of the ribs is sufficiently reduced, and the tendency of these structures to obscure underlying pulmonary tissues is almost wholly alleviated. This trend may be expected to continue.

Miscellaneous Factors Affecting Image Quality (also, see Table I-57)

This discussion of the technical aspects of chest radiography would be incomplete without mentioning the importance of a number of tech-

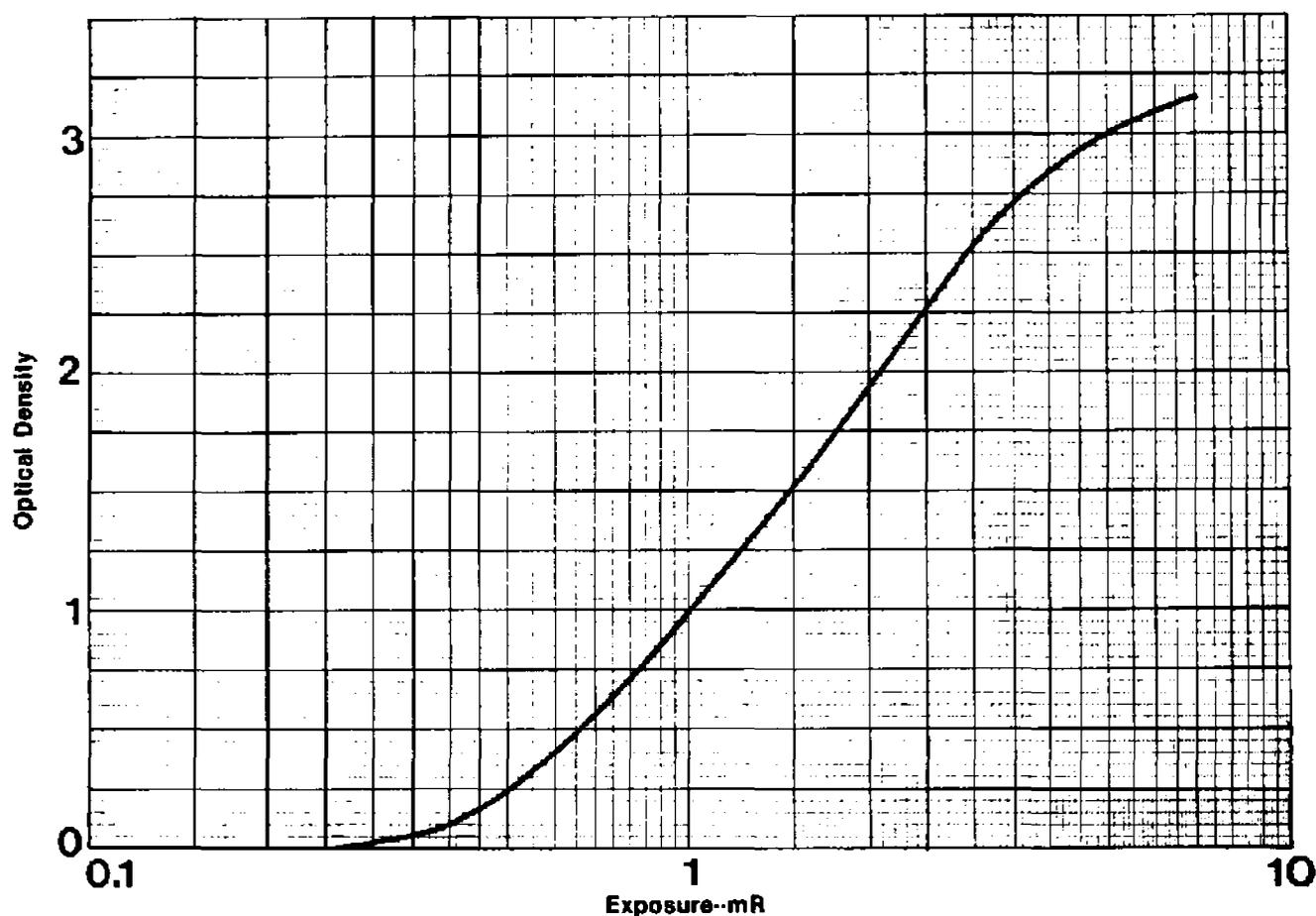


Figure I-15. Relationship between the exposure received by a typical film-screen combination and the optical density or blackness of the processed film.

Table I-57
CRITERIA FOR EXCELLENCE OF TECHNICAL
QUALITY IN CHEST RADIOGRAPHS

The following rules may be helpful to those seeking technical excellence in radiography of the chest:

A. Optical Density

1. Hilar regions should exhibit a minimum of 0.2 units of optical density above fog.
2. Parenchymal regions should exhibit a maximum of 1.8 units of optical density above fog.

B. Gross Image Contrast

The difference in optical density between the darkest segment of the lung parenchyma and the lightest portions of the hilar region should fall within a range of 1.0 and 1.4 units of optical density.

C. X-ray Tube Potentials and Use of Grids

1. Potentials of 70 to 100 kVp: Use grid for all subjects whose posteroanterior dimension exceeds 22 cm.
2. Potentials over 100 kVp: Use grid for all subjects.

D. Exposure time: Not greater than 0.1 sec., and preferably 0.05 seconds or less.

E. Film-Screen Combination: Use medium-speed films and screens to assure adequate image detail. Good screen-film contact is essential; periodic testing mandatory.

F. Processing: Maintain strength and temperature of processing chemicals within limits recommended by manufacturer.

G. Assumptions

1. Cleanliness of films and screens and of processing fluids and equipment is maintained.
 2. Care in subject positioning is taken.
 3. Subject movement is prevented.
-

nical requirements that must be met for the attainment of optimum image quality. One is the respiratory phase of the patient when a chest radiograph is made. It is essential that the patient be in deep inspiration with respiration arrested. This is to maximize image clarity and contrast and to reduce patient exposure. Films exposed during expiration or shallow inspiration are almost always unacceptable.

Another requirement concerns the position of the patient during exposure. He or she should be upright and placed facing the cassette in such a way that all portions of the lung fields, including the apices of the lungs, the lateral chest walls and the costophrenic angles, are recorded on the film. Moreover, the shoulders must be rotated forward so that the scapulae are moved to the sides and away from positions in which they obscure the lung fields.

Darkroom cleanliness and adherence to strict time-temperature processing is elementary but fundamentally important. All too often

radiographic films are spoiled by poor darkroom technique. The repeated films occasioned by such spoilage represent the worst kind of unnecessary radiation exposure; radiation that with disciplined darkroom practices can be avoided entirely.

**Major Problems
in the Radiographic Technique**

Experience gained from the pneumoconiosis programs of the National Institute for Occupational Safety and Health and of the Department of Labor, indicates that the most serious problem found by physicians and their technologists in producing satisfactory films of the chest is the estimation of proper radiographic exposure. There is little room for error when such estimates are made; overexposure or underexposure, with resultant loss of image quality, can easily occur.

The correction of this problem lies in improved training programs for both physicians and technologists. The need for professional ex-

cellence in radiographic technology cannot be overemphasized. Unfortunately, many of radiology's practitioners currently fail to recognize its importance.

Another technical problem, almost as serious as that pertaining to radiographic exposure, is the inadequate control of scattered radiation, particularly in large patients. Since satisfactory methods of control are readily available, this problem's correction seems to be a matter of improved training and supervision of radiographic professionals. When scattered radiation is not controlled properly, image contrast falls quickly to unacceptable levels.

Three other technical problems also reflect inadequate radiographic skills and/or lack of professional discipline and supervision among physicians and their technologists: unsatisfactory patient positioning, failure to correct radiographic cassettes in which there is poor film-screen contact, and failure to maintain minimum standards of cleanliness in the darkroom.

Taken together, these problems cause—in the best of settings—about 10% of chest radiographs to fall below optimal quality standards. In the worst situations, failure rates exceeding 50% are not uncommon.

STANDARDS OF INTERPRETATION AND CLASSIFICATION OF CHEST RADIOGRAPHS IN PNEUMOCONIOSIS

The Radiology of Pneumoconiosis (5)

When dusts containing one or more of the many compounds of silicon are inhaled, pathological changes occur within the lungs and pleural coverings that are detectable radiographically. As the dust particles find their way into the lungs' alveolar sacs, a localized reaction takes place about each particle or group of particles that ultimately leads to the formation of a small fibrous nodule. Such nodules appear in the lung fields of a chest radiograph as small discrete opacities, rounded and/or irregular in shape, a few millimeters in diameter, and distributed widely throughout the lungs.

When dust exposure is limited, the number or profusion of opacities is likely to be small and their distribution localized. However, if the exposure continues, the opacities will increase in number until ultimately, adjacent lesions coalesce to form large opacities several centimeters

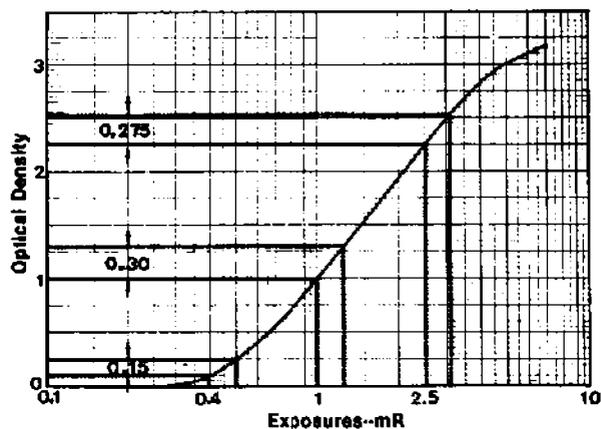


Figure I-16. Illustration of the effect of optical density on the contrast exhibited by an image recorded by a radiographic film.

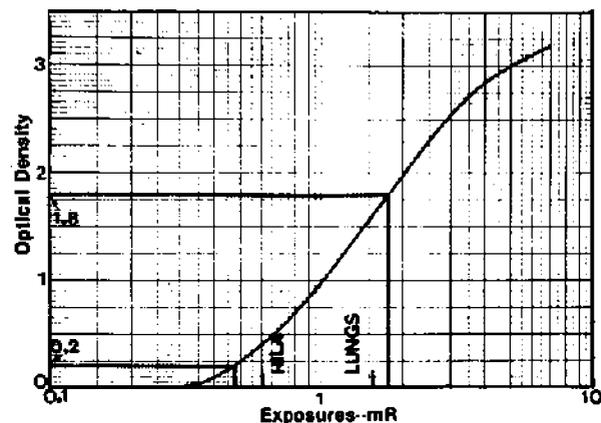


Figure I-17. Graphic illustration of how the latitude of a technologist in estimating the exposure to be given during radiography of the chest diminishes as the useful range of optical density becomes increasingly filled by images of diagnostic interest.

in diameter and often distributed widely throughout the lungs. At this stage, serious lung damage has occurred.

With many silicic materials, such as those encountered in coal mining, radiographic opacities tend to reside in the upper lung fields. In other cases, especially when asbestos fibers are inhaled, changes are more commonly observed in the lung bases and are more irregular or linear in shape. Asbestos fibers tend to migrate to pleural surfaces by way of lymphatic channels to create localized fibrous thickenings of pleural tissues. These lesions characteristically occur

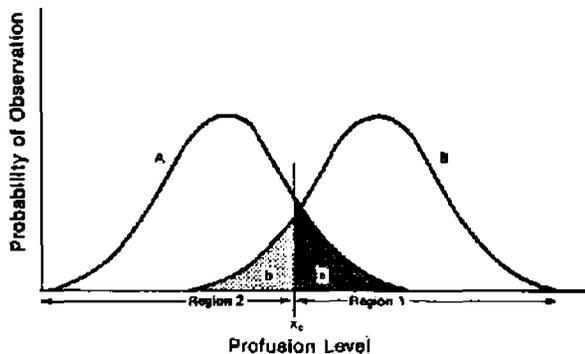


Figure I-18. Representation of the decision problem in pneumoconiosis. Hypothetical population distributions in which the ordinate depicts the probability of one's observing a given profusion level in a population free of pneumoconiosis (curve A) and in a population with pneumoconiosis (curve B).

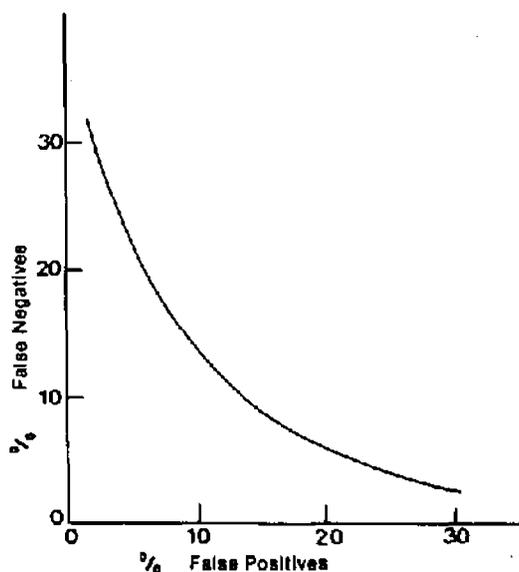


Figure I-19. Curve illustrating reciprocal relationship between percentage false negative and false positive interpretations of chest radiographs for pneumoconiosis (derived from data given in Figure I-18).

along lower chest walls, on diaphragmatic surfaces, and in pleural and pericardial surfaces adjacent to the heart. Frequently, they become calcified.

In advanced cases of pneumoconiosis, there is usually no question, radiographically, regarding the disease's diagnosis. However, when only small opacities are present and their profusion is limited, interpretation can be difficult (12).

This is because small opacities can occur in a wide variety of situations, both normal and abnormal, as well as in pneumoconiosis. For example, as individuals become older, periodic respiratory infections often leave them with pulmonary fibrotic changes that appear radiographically as small irregular opacities. These changes are particularly prevalent in cigarette smokers. Also, individuals who suffer from congestive heart disease, in time, develop extensive fibrotic findings in the lungs that may be confused with early stages of pneumoconiosis. Finally, many pathological conditions unrelated to dust (e.g., sarcoidosis) manifest, at various times in their courses, radiographically as small opacities.

So radiographic findings in early pneumoconiosis are not unequivocally interpretative. This has led to the suggestion that chest radiographs always be evaluated with the assistance of the clinical information provided in the patient's history. Superficially, the suggestion appears to have merit. However, it must be recognized that such clinical data usually exhibit as many uncertainties as the radiographic findings. Hence, it is wise in most instances to evaluate history and radiography independently of one another and only afterward bring the two bodies of information together for a clinical judgment. Such a process tends to maximize clinical objectivity and minimize interpretative errors of the history and radiographic information.

Because of the difficulties that exist in the interpretation of chest radiographs, it is not surprising that inconsistencies arise when a number of physicians independently evaluate a series of radiographs or when an individual physician evaluates the series a number of times. Such inconsistency is unavoidable and indeed is characteristic not only of radiographic procedures but all clinical testing (including history taking, physical examinations, and physiological tests) due to uncertainties inherent in all methodologies in which human judgment is a factor (8)(19).

To illustrate graphically the manner in which interfering patterns affect the decision processes and observer error in the interpretation of chest radiographs for pneumoconiosis, consider the profusion of small rounded or irregular opacities (i.e., the number of opacities per cm^2) that might be observed in the films of

a representative sample of individuals who are free of the disease: Curve A, Figure I-18, plotting the number of films prevailing at each profusion level, depicts data that might result from such a study. The profusion of similar opacities in the radiographs of individuals who have pneumoconiosis are greater; the corresponding probability distribution generated by those cases might be characterized by Curve B. The two curves overlap and diagnostic uncertainty will prevail for cases included in the overlapping region. If an interpreter selects a profusion level of x_c as his operating point—separating cases he will call positive for pneumoconiosis from those he will call negative—cases to the right of x_c in region 1 will be called positive for the disease. Of these, the cases under the unshaded portion of Curve B will be correctly diagnosed; i.e., they will be true positives. However, cases included under the shaded portion of Curve A (a) will also be called positive, in spite of the fact that they actually are free of the disease. Such cases will, therefore, be false positives.

Cases to the left of x_c in region 2 will be interpreted as normal. Of these, cases under the unshaded portion of Curve A will be correctly diagnosed as negative, whereas those under the shaded portion of Curve B (b) must represent false negative interpretations, since disease is actually present in these cases.

It will be evident from an examination of Figure I-18 that the percentages of false positive and false negative interpretations will depend upon where the operating point (x_c) is placed. If it is placed to the left of the position shown, the number of false negatives will diminish but at the expense of an increasing number of false positives. If the operating point is moved to the right, the number of false positives will diminish but at the expense of an increasing number of false negatives. The reciprocal relationship between the percentage of false positive and false negative interpretations as one moves the operating point (x_c) along the profusion axis is illustrated graphically in the Figure I-19.

Significant inconsistencies among readers in the radiographic interpretation of pneumoconiosis have been documented (1)(2)(6)(7)(16)(17). Reger found that three American readers who interpreted 498 coal miners' radiographs of profusion according to the UICC Classification agreed as to the major x-ray category on 48% to

71% of the films, while on these same films five British readers agreed on 83% to 90% (3)(16). Felson similarly documented the level of agreement among readers who interpreted the radiographs of 55,730 coal miners examined under the Federal Coal Mine Health and Safety Act of 1969. Felson found the 'A' readers (the first readers to interpret the miner's X-ray) agreed with 'B' readers (members of radiology departments at three hospitals who were experienced at classifying pneumoconiosis) on 41,493 (74.5%) of the 55,730 films interpreted. In both Reger's and Felson's studies approximately 87% to 89% of the films were interpreted as normal.

Inconsistencies in radiographic interpretation can probably be reduced by multiple readings carried out independently by a number of physicians with results examined for consensus (18). Inconsistency can also be minimized by training programs in which physicians are taught to recognize subtle differences between normal and abnormal radiographs. Finally, it is important that physicians responsible for interpreting chest radiographs in national pneumoconiosis programs have opportunities to apply their knowledge sufficiently often to maintain diagnostic acuity. If these criteria are carefully observed, the chest radiograph can be relied upon to be of great value in the evaluation of individuals suspected of having dust-related disease.

ILO Classification System (9) (11)

In clinical practice, it is customary for physicians reporting radiological findings recorded in chest films to do so in nonquantitative, narrative form. For most clinical purposes this is satisfactory. However, when the information is to be used epidemiologically or to evaluate pulmonary disability in workmen's compensation programs, the reporting must be more quantitative.

The need for this was first recognized officially by the International Conference on Silicosis held in Johannesburg in 1930. Since then, the system devised during that meeting has evolved through a series of revisions until the current system, known as the ILO 1980 International Classification of Radiographs of the Pneumoconioses, was recently adopted by the International Labor Office in Geneva (9). The current system has been designed not only to permit codification of coal workers' pneumoconiosis (CWP) and silicosis but also of asbestosis. Ex-

pansion of the system to include the latter entity occurred in 1967 with the assistance of a subcommittee of the Committee on Asbestos and Cancer of the International Union Against Cancer (UICC), members of the McGill University Asbestos Study, and the panel of Radiology Consultants to the Bureau of Occupational Safety and Health, U.S. Public Health Service (USPHS) meeting in Cincinnati.

The ILO-80 Classification System requires the codification of a chest radiograph according to its pulmonary and pleural findings and to its technical quality. With respect to pulmonary findings, the system divides lung opacities into two categories: small and large with each defined in specific quantitative terms.

Small Opacities

The system requires the recording of data on the following four characteristics: shape, size, profusion, and extent. Two shapes are recognized; small rounded and small irregular. For each shape, opacity size is graded in three categories. For example, rounded opacities are classified according to the approximate diameter of the predominant lesions into:

- (p) opacities up to about 1.5 mm in diameter
- (q) opacities exceeding 1.5 mm and up to about 3 mm in diameter
- (r) opacities exceeding about 3 mm and up to about 10 mm in diameter

Irregular opacities are classified according to the approximate width of the predominant lesions into:

- (s) fine linear opacities up to about 1.5 mm width
- (t) medium opacities exceeding about 1.5 mm and up to about 3 mm in width
- (u) coarse, blotchy opacities exceeding about 3 mm and up to about 10 mm in width

To record shape and size, two letters must be used. If the reader considers that virtually all of the opacities are of one shape and size, this should be noted by recording the appropriate symbol twice, separated by an oblique stroke (e.g., q/q). If, however, another less predominant shape (or size) is observed, this should be recorded as the second letter (e.g., q/t). Hence, q/t would mean that the predominant small opacity is round and of a size q, but that significant numbers of small irregular opacities are pre-

sent of size t. In this scheme, the recording of no more than two kinds of size and shape is permissible.

The term profusion refers to the concentration or number of small opacities per unit area observed within the lung fields. In early versions of the system, profusion was graded only in four major categories:

Category 0: small opacities are absent or less profuse than Category 1

Category 1: small opacities are present, but few in number; the normal lung markings (i.e., the images of the vascular structures) are usually visible

Category 2: small opacities are numerous; the normal lung markings are partially obscured

Category 3: small opacities are very numerous; normal lung markings are usually totally obscured

In 1968, this codification of small-opacity profusion was modified by the further division of each major category into three minor divisions to provide a 12-point scale or continuum. The current notation designating the several divisions of this scale is as follows:

0/-	0/0	0/1
1/0	1/1	1/2
3/2	3/3	3/+

The first number in each division indicates the major category to which the division belongs; the second number indicates whether the profusion level is judged to be somewhat less than, equal to, or somewhat greater than the profusion level corresponding to the major category indicated. Thus, the notation 2/1 is used to indicate a profusion level that is definitely category 2 but somewhat less than the midpoint of that major category.

Although this 12-point scale of profusion implies a high degree of quantification for the recording of profusion levels, the definition of the major profusion categories on which the scale is based is nonspecific. Hence, when the profusion levels of a series of radiographs are evaluated by a group of physicians, substantial differences of opinion can be expressed.

The problem is particularly bothersome when profusion levels are near the lower end of the scale. This is because films in major category 0

(i.e., profusion categories 0/–, 0/0, and 0/1) are usually regarded as normal or as exhibiting essentially no evidence of pneumoconiosis, whereas films in major category 1 (i.e., profusion categories 1/0, 1/1, and 1/2) are generally regarded as positive for pneumoconiosis. The radiological findings of pneumoconiosis in its early stages are difficult to differentiate from the findings of normal individuals. Both may have similar small-opacity profusion levels. Physicians generally have difficulty in separating a series of radiographs into normals and abnormal when profusion levels are near the divisions 0/1 and 1/0. A given physician will exhibit some inconsistency in his or her codification of profusion in such instances.

Physicians of limited experience, or physicians who do not have the opportunity to see (in their practices) the range of appearance normal films may exhibit, tend to codify their films into higher profusion levels than those classified by their more experienced colleagues. This circumstance constitutes a serious problem for administrators of workmen's compensation programs because consistency between readers is difficult to obtain when readers of different backgrounds and experience interpret films. It is a problem that can be resolved only by the development of improved training standards for all physicians involved in such programs and by the use of multiple readings to resolve interpretive differences when they occur.

The fourth characteristic of small opacities that must be codified in the ILO-80 Classification System is the spatial distribution of pulmonary disease. To record this parameter, lung fields are divided into six zones, three on each side, corresponding to the upper middle and lower thirds of the lung fields. In reporting the extent of disease, the physician simply checks off the zones affected.

Of the four characteristics of small opacities requiring codification, profusion is the most important for it is the best indicator of the seriousness of any disease that may be present. When profusion levels vary from one portion of the lung fields to another, the category of profusion to be recorded is determined by considering the profusion as a whole, over the affected lung zones. Where there is a marked (three minor categories or more) difference in profusion in different zones, the zone or zones showing the lesser degree of profusion are ignored for the

purpose of classifying profusion.

Large Opacities

These lesions are codified in three categories of size:

Category A: a single opacity whose greatest diameter exceeds about 1 cm but is no more than about 5cm, or several opacities, each greater than about 1 cm in diameter, the sum of whose diameters does not exceed about 5 cm.

Category B: one or more opacities larger or more numerous than those in Category A whose combined area does not exceed the equivalent of the right upper zone.

Category C: one or more opacities whose combined area exceeds the equivalent of the right upper zone.

Pleural Thickening

With respect to pleural thickening, the ILO-80 Classification System requires that the site (chest wall, diaphragm, costophrenic angle), width, and extent of the thickening be recorded separately. In the case of site, pleural thickening of the chest wall must be recorded separately for right and left sides.

For pleural thickening observed in profile (edge on), width is measured from the inner border of the chest wall to the inner margin of the parenchymal-pleural boundary seen most sharply. The ILO system recognizes three gradations of width:

- a. a maximum width up to about 5 mm
- b. a maximum width over about 5 mm and up to about 10mm
- c. a maximum width over about 10 mm

The presence of pleural thickening observed face on (en face) is recorded even if it cannot be seen in profile. If pleural thickening is observed face on only, width cannot be measured.

The extent of pleural thickening is defined in terms of its maximum length, whether seen in profile or face on. Three gradations of extent are recognized:

1. total length equivalent to up to one quarter of the projection of the lateral chest wall.
2. total length exceeding one quarter but not one half of the projection of the lateral chest wall.

- total length exceeding one half of the projection of the lateral chest wall.

With respect to involvement of the diaphragmatic pleura, localized thickening (plaque) is recorded separately as present or absent, and right and/or left. Obliteration of the costophrenic angle is recorded in a similar manner.

When pleural calcification is observed, its site (chest wall, diaphragm, and other locations) and extent are recorded separately for the two sides of the thorax. Three gradations of extent are recognized:

- a region of calcified pleura with a maximum diameter of up to about 2 cm or a number of such regions, the sum of whose diameters does not exceed about 2 cm.
- a region of calcified pleura with maximum diameter exceeding about 2 cm and up to about 10 cm, or a number of such regions, the sum of whose maximum diameters falls within this range.
- a region or number of regions of calcified pleura, the sum of whose maximum diameters exceeds 10 cm.

Obligatory Symbols

The ILO Classification System includes a number of symbols (whose use is obligatory) to permit the recording of important radiographic features (see Table I-58).

Technical Quality

The ILO Classification System recognizes four gradations of technical quality as follows:

- Good
- Acceptable, with no technical defect likely to impair classification of the radiograph for pneumoniosis
- Poor, with some technical defect but still acceptable for classification purposes
- Unacceptable

If the technical quality of a radiograph is not Grade 1, the technical defects should be commented upon.

Standard Radiographs

To enhance consistency in the application of its classification system, the ILO has made available to physicians sets of standard chest

Table I-58

OBLIGATORY SYMBOLS

ax	—coalescence of small pneumoconiotic opacities
bu	—bullae
ca	—cancer of lungs or pleura
cn	—calcification in small pneumoconiotic opacities
co	—abnormal cardiac size and/or shape
cp	—cor pulmonale
cv	—cavity
di	—marked distortion of intrathoracic organs
ef	—effusion
em	—definite pulmonary emphysema
es	—eggshell calcification of hilar or mediastinal lymph nodes
fr	—fractured rib(s)
hi	—enlargement of hilar or mediastinal lymph nodes
ho	—honeycomb lung
id	—ill-defined diaphragm
ih	—ill-defined heart outline
kl	—septal (Kerley) lines
od	—other significant abnormality
pi	—pleural thickening in the interlobar fissure or mediastinum
px	—pneumothorax
rh	—rheumatoid pneumoconiosis
tb	—tuberculosis

radiographs, which illustrate various stages of pneumoconiosis and which have been codified by an international panel of experts. These films provide examples of the classification system and are useful for comparison purposes when a physician examines a series of chest films. The availability of these standard films has been an important contribution to occupational medicine. They may be obtained in the United States at a cost of \$275 per set from the International Labour Organization, 1750 New York Avenue, NW., Washington, DC. 20006.

Full size reproductions of pertinent sections of the standard films are illustrated in Figures I-15 through I-19. These examples provide graphic demonstrations of small opacity profusion, size, and shape, and attributes of large opacities and pleural thickening defined in prior sections of this chapter.

TRAINING OF PHYSICIANS AND TECHNOLOGISTS

The usefulness of any medical procedure is markedly dependent upon the skills of the individual performing the technical work involved in the procedure and of the physicians who interpret the procedure's derived information. For that reason, the National Institute for Occupational Safety and Health (NIOSH) has been vitally interested in the training and professional standards of physicians and radiographic technologists who participate in its pneumoconiosis programs. For many years, NIOSH, with the assistance of the American College of Radiology, has provided radiologists, chest physicians, occupational health specialists, and their associated technologists short courses (of several days' duration) designed to improve the skills of these individuals both in producing and classifying chest radiographs. The courses are offered at frequent intervals throughout the United States to enable as many individuals as possible to take them.

Courses designed for physicians have been particularly effective. Over 2,500 doctors in a variety of specialties have attended these courses since their inception in the early 1970's. Those who attend one or more of the courses are designated as "A" readers by NIOSH. All of the physicians who participate in its pneumoconiosis programs are "A" readers.

At about the time its training programs for physicians were begun, NIOSH, as well as the Social Security Administration, began the practice of multiple readings of chest radiographs submitted to them by coal workers seeking benefits under the 1969 Federal Coal Miners Health and Safety Act (PL 91-713). Although this practice has been frequently misunderstood, it was instituted with the single purpose of improving the validity of medical information gained from these radiographs. Physician inconsistency can occur in the interpretation and classification of chest radiographs for pneumoconiosis; one of the methods by which such inconsistency can be reduced is the process of multiple readings of films. It is a meritorious practice: it not only benefits the coal miner by increasing the value of information provided by his chest radiograph, it also protects the public against fraudulent reports of disease that are occasionally submitted for adjudication. For these reasons, the practice of multiple reading has been mandated by

NIOSH regulations.

In an effort to assure that readings of coal workers' chest films are performed by physicians having the highest possible credentials, NIOSH, in 1973, contracted the Johns Hopkins School of Medicine to develop an examination the Institute could use to test the proficiency of physicians employing the ILO Classification System. Since that time, the examination has been given to over 200 physicians, about 120 of who have been given passing (i.e., 50 or better) grades (13). Those who have passed are called "B" readers and, unless their skill decays from disuse, collectively constitute a superb resource of established competence, available for the evaluation of the increasing number of chest radiographs of individuals who may have been occupationally exposed to hazardous levels of inorganic dusts.

Periodically, the merits of using properly trained lay persons to classify chest radiographs in accordance with the ILO system are considered. If this were practical, it would reduce the burden on physician manpower and might reduce costs. A number of experiments have been carried out to determine the effectiveness of such readers after an appropriate training period. The results of these tests are encouraging. In a recent experiment in the United Kingdom, a group of lay readers, after a period of one year's training, performed as well as a group of experienced physician cohorts (10).

Although training programs developed to augment physician proficiency in the use of the ILO Classification System have been successful, the same cannot, regretfully, be said of efforts to improve the skills of technologists in producing chest radiographs of consistently high quality. Currently, upward of 10% to 25% of the chest films submitted to the Department of Labor and the Social Security Administration are unreadable for technical reasons and many more are less than satisfactory. This is particularly reprehensible because a high proportion of readable films can be achieved given proper equipment, training, and administrative control.

The problem is not only a matter of technologist skill, but of the supervision technologists receive from physicians for whom they work. Since many physicians, including radiologists, receive little or no training in the technical aspects of radiography, their supervision is often of doubtful value. The problem is particularly serious because the radiographic characteristics

of the human chest are such that a technologist has precious little latitude for error in estimating the proper exposure to be given a particular patient during chest radiography.

Much greater effort must be expended on radiographic technology training, not only for the technologist, but for the radiologist and practicing physician who uses radiographic equipment as well. All government agencies having responsibility for the administration of coal workers' benefits must establish, as rapidly as possible, minimum technical standards for personnel who wish to provide chest radiographs to them. Some years ago, NIOSH developed and implemented the use of a series of standards which have been instrumental in substantially reducing the number of unreadable films submitted to it (less than 1%). Other government agencies, which have not yet established similar standards of acceptability, should do so with all deliberate speed. Without such efforts, and the will to apply them rigorously, coal workers, as well as the taxpaying public, will continue to suffer inconvenience and loss.

OTHER RADIOGRAPHIC TECHNIQUES USEFUL IN THE EVALUATION OF PNEUMOCONIOSIS

Limitations of Conventional Radiographic Methods

Radiographic methods primarily record anatomical structure. With limited exception, they do *not* record function. Information provided by a chest radiograph on lung structure and on pathological changes that may exist within them is more useful than information on how the lungs may be functioning. In short, the chest radiograph is better in evaluating pathological characteristics of disease than in assessing any impairment the disease may have caused.

These limitations of chest radiography in the evaluation of pulmonary impairment are not difficult to understand. In pneumoconiosis, the disease, particularly in its early stages, is frequently confined to small portions of the lungs (e.g., the upper lobes); large segments can be relatively unaffected. Unaffected regions are likely to function reasonably well, and therefore, regardless of how extensive the disease may be in the diseased zone, pulmonary function may not be significantly impaired. On the other hand,

there are times when the disease initially involves much of the lung parenchyma with fibrotic changes that may not be impressive radiographically, but because they are so widespread, may impair function and cause disability relatively early.

The physiological limitations of the chest radiograph should in no way deprecate its value—either from a clinical or public health standpoint—in the evaluation of persons suffering from pneumoconiosis. Its objectivity in accurately and reliably assessing the disease's pathological anatomy is unequalled. Often it represents the best data available on the clinical status of a patient.

Other Radiographic Techniques

The simple chest radiograph, taken with the radiation projected through the subject in a posterioranterior direction, is the keystone of all radiographic examinations of the chest. However, there are occasions when a more extensive examination is called for. For instance, pleural thickening can be detected most easily when seen in profile. Therefore, when localized thickenings exist, as is frequently the case in asbestosis, it may be desirable to take oblique and lateral views of the chest in an effort to bring the lesion into profile.

When pneumoconiosis is complicated by co-existing disease, there are additional radiographic measures that may be useful in evaluating the nature and extent of the pathological processes and their relationships. One of these is tomography, a technique in which thin slices of pulmonary tissues are recorded in cross-section or longitudinally. The images may be presented either in conventional or computerized form. When many such films are made, each depicting a different section of the lungs, pulmonary architecture can be displayed in remarkable detail and without the confusing, superimposed patterns of other structures. The technique is particularly valuable when pulmonary cavities and masses are to be evaluated.

Another technique, useful in the evaluation of bronchial disease, is bronchography. In this procedure, radiopaque materials are instilled or blown into the bronchial tree to demonstrate irregularities, dilations, and obstructive lesions of the respiratory system.

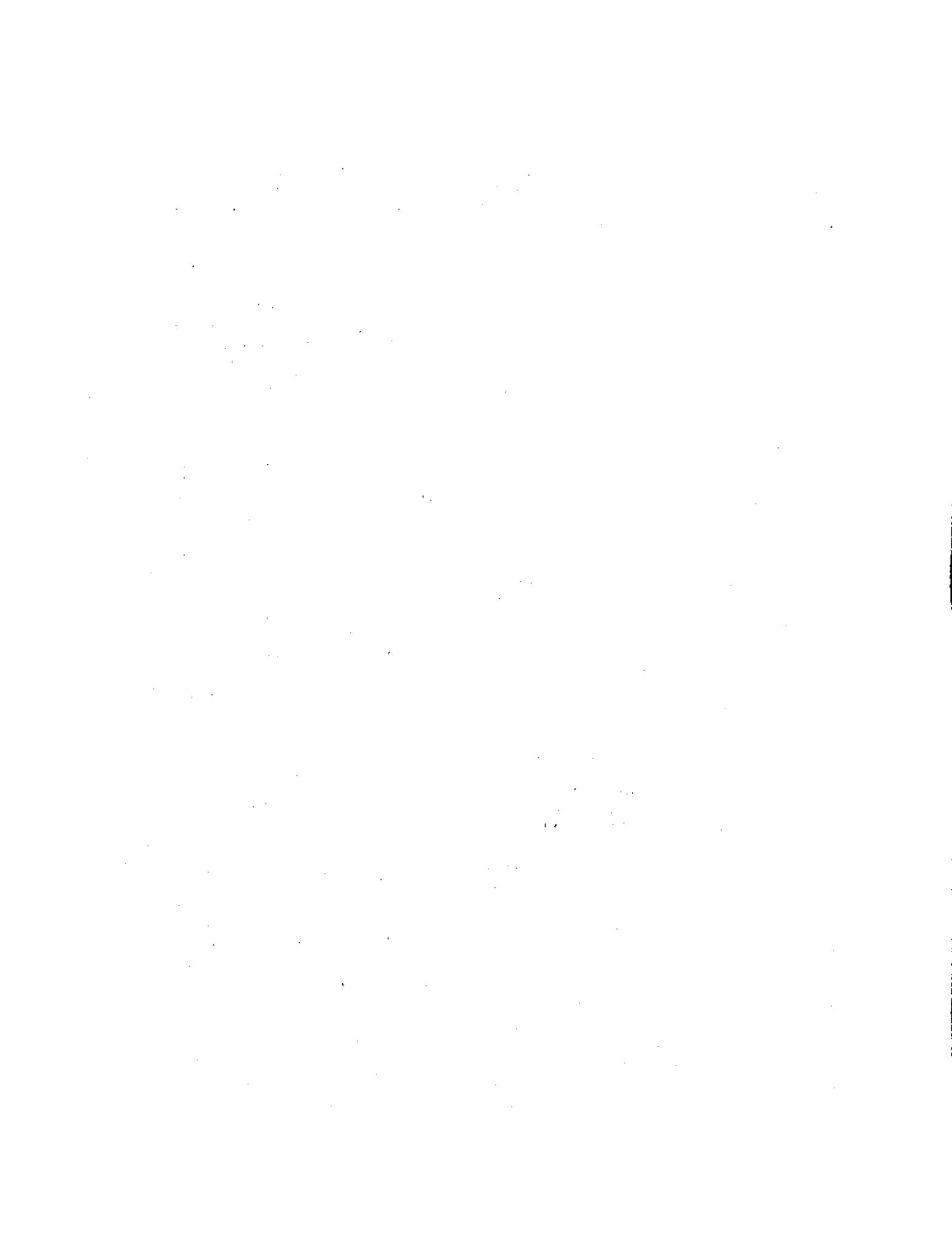
Finally, a battery of radiological tests employing radioactive nuclides has been devised in recent years to study vascular problems associ-

ated with the lungs. Some of these show promise in the evaluation of pulmonary function.

All together, radiologic procedures constitute an enormously valuable group of diagnostic tools for use by clinicians and public health physicians when dust-related occupational disease is evaluated. One may expect the number and scope of these techniques to become even greater in the years ahead as medicine profits from this fast-growing science.

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PULMONARY FUNCTION TESTING

Benjamin Burrows

Pulmonary function studies are an essential part of any respiratory evaluation. Capable of detecting abnormalities not evident on chest radiography and not associated with symptoms, lung function tests are relatively objective and provide a quantitative index of impairment. They are invaluable for investigating dose-effect relationships, for studying progression of abnormalities, and for evaluating disability. Some individual lung function studies are specific for particular types of lung alterations and are thereby useful in determining the mechanism of a noxious agent's effect.

Critical to pulmonary function testing is the expertise of the staff administering the tests. The capabilities of the pulmonary function technician can often determine the accuracy of test results. It is also essential that standardized procedures be used and that tests of quality control be included whenever lung function studies are carried out.

CONSIDERATIONS IN THE SELECTION OF TESTS

A large number of lung function tests are available. They measure different aspects of lung function and vary greatly in complexity. Some of the more commonly used tests are listed in Table I-59. Some are readily applicable to epidemiological studies; others are restricted to in-laboratory studies of small groups of selected subjects.

Determining the mechanism of a known noxious agent's action in affected subjects may require pressure-volume curves to assess a loss of lung recoil from emphysema or a decrease in compliance owing to diffuse fibrotic changes. Studies of airways resistance may be needed to determine the extent and localization of airways abnormalities. However, since complete evaluation of lung mechanics requires an esophageal balloon and relatively sophisticated technology, these tests are not applicable to epidemiological

investigations.

Arterial blood gas measurements provide less specific information about disease mechanisms but are useful in disability evaluations. Arterial oxygen and carbon dioxide tensions provide important information about the physiological impact of disease. The use of arterial blood gases in epidemiological studies is limited, however, by the wide intrasubject variability of arterial oxygen measurements, as well as by the need for arterial puncture which involves some patient discomfort and a small risk of complication (42).

The Timed Spirogram

The forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) are the simplest, most reproducible, and most widely employed lung function tests. They primarily reflect the mechanical function of the lung and have been regarded as essential for all respiratory epidemiological studies (14). To perform these tests, the subject takes a deep inspiration and then exhales as rapidly and completely as possible into a recording device. A "timed spirogram" is thus obtained. It is recommended that at least three technically satisfactory tests be recorded and that the maximum values for FEV₁ and FVC be reported (14). Recently published recommendations in regard to instrumentation and test procedures are summarized in Table I-60 (14)(36). Traditionally, the test has been carried out with a relatively inexpensive, internally calibrated instrument—such as a water-sealed spirometer recording on a simple kymograph. Measurements are then made from the obtained tracings by a technician.

Measurement errors may be eliminated and the procedure simplified by automated analyses (using computer technology). A variety of electronic devices are available which are easier to use and more portable than the traditional water filled spirometer. While automated measure

Table I-59
SUMMARY OF LUNG FUNCTION TESTS

- A. Minimal tests, useful for detecting abnormalities in groups or in individuals:
Timed spirometry with measurement of FVC and FEV₁
(Measurement of FEF 25-75% optional)
 - B. Sensitive tests, useful for detecting subtle abnormalities in groups but of questionable significance in individuals:
 - 1. MEFV curve with measurement of Vmax_{50%} and Vmax_{25%}
 - 2. Closing volume test with measurement of CV/VC and Slope III
 - C. Tests especially useful for detecting diffuse interstitial diseases:
Single breath diffusing capacity
 - D. Tests used primarily in disability evaluations:
 - 1. Arterial blood gases at rest and exercise
 - 2. Maximum voluntary ventilation
 - E. Tests which may be useful for determining the nature of a physiological abnormality but not generally recommended for population surveys:
 - 1. Total lung capacity measurements
 - 2. Pressure-volume curves with measurements of lung compliance and recoil
 - 3. Airways resistance measurements
 - 4. Helium vs. air MEFV curves
 - F. Tests for determining the degree of airways reactivity:
 - 1. Methacholine or histamine inhalation challenge
 - 2. Exercise provocation test
-

ments and newer recording devices have many desirable features, they do impose the need for careful apparatus calibration. Also, special consideration must be given to determining the onset of the test in a manner analogous to the "back extrapolation method" used in hand calculations (14). Algorithms to accomplish this have been reported both for volume (39) and flow sensitive devices (22).

The FEV₁ and FVC are highly reproducible within individuals; show little variation with time of day or season; and involve relatively little subject cooperation or discomfort (42). Generally, an inadequately performed test is immediately recognized by an experienced technician. A complete study can be performed within five to ten minutes, and tests are readily performed in the field.

As with virtually all lung function tests, there is wide intersubject variability in test results. Much of this is related to the age, sex,

and body size of subjects and can be accounted for by prediction formulae. However, even among totally asymptomatic nonsmoking subjects in the general population, obtained data show a standard deviation of approximately 15% around predicted values (22). Also, the FEV₁ and FVC tests may not detect very mild changes in the airways, changes which can be detected by more "sensitive" tests of lung function.

Additional data are available from the maneuver carried out to obtain the FEV₁ and FVC. The average flow over some segment of the forced exhalation (e.g., between exhalation of 25% and 75% of the FVC (FEF 25-75%)) can be measured. It has been claimed that the FEF 25-75% is more sensitive than the FEV₁, but newer data refute this (14). Nevertheless, since determination of the FEF 25-75% requires no additional effort or time on the part of the subject; no additional instrumentation; and little ex-

Table I-60
STANDARDS FOR SPIROMETRIC TESTING

A. Instrument

1. Minimum usable volume $7 + L$. (for volume sensitive devices).
2. Must measure volume with an error $\pm 3\%$ of reading or ± 50 ml, whichever is greater.
3. Must be able to accumulate volume for $10+$ seconds.*
4. Must produce a graphic record of volume vs. time or of volume vs. flow for the entire forced expiration.
5. Time display must be $2 +$ cm per second, volume display at least 10 mm per liter, and flow at least 4 mm per L/sec.
6. A volume sensitive device should be equipped with a thermometer.
7. The recorder must have reached calibrated speed by the onset of the forced expiration.

B. Test Procedure

1. Nose clips are needed with closed circuit testing.
2. At least three apparently satisfactory tracings must be obtained and the FVC and FEV_1 of the best two should vary by no more than 5% of reading or 100 ml, whichever is greater.
3. The largest FVC and FEV_1 are reported even if they do not come from the same maneuver.

*This is deemed adequate for field work but not for clinical studies. Clinically ill subjects may not complete their expiration by 10 seconds (14).

tra effort in calculation, the test has been recommended for epidemiological investigations (14).

The Maximum Expiratory Flow-Volume Curve

Still more information may be procured if data obtained during an FVC maneuver is displayed as a maximum expiratory flow-volume (MEFV) curve, plotting instantaneous flow (\dot{V}_{max}) against volume exhaled. The flow after exhaling half of the FVC (\dot{V}_{max} 50%) is generally measured. It is closely related to the FEF 25-75% and has about the same sensitivity (20). Flow later in expiration, as when only 25% of the FVC remains to be exhaled (\dot{V}_{max} 25%), should detect more subtle abnormalities. The small airways contribute a greater fraction of the total airflow resistance at low lung volumes, and abnormalities resulting from inhaled irritants often begin at the level of these small airways. Also, preferential slowing late in expiration would be expected, regardless of the site of disease, since

almost all abnormalities develop in a nonuniform fashion, and the most obstructed, slowest emptying regions are preferentially represented late in the MEFV curve.

The \dot{V}_{max} shows increasing variability late in the MEFV curve. The standard deviation around predicted of the \dot{V}_{max} 25% is in the range of the 30% in asymptomatic nonsmokers (22), and intrasubject variability is much higher than for the FEV_1 (42). Despite its variability, the \dot{V}_{max} 25% does reveal a greater number of abnormalities in smokers and in symptomatic subjects than does the FEV_1 , and it may have a role in the detection of mild airways abnormalities (19).

In measuring the \dot{V}_{max} 25%, it is essential that a complete expiration be obtained. Failure to empty the chest fully will affect the point at which \dot{V}_{max} 25% is measured and may lead to a falsely high value. The possibility of a falsely high value exists with any flow measurement made at a given fraction of the FVC (or expressed

as a fraction of FVC) including the FEF 25-75%, any V_{max} measurement, and the FEV_1/FVC ratio. With the FEV_1 or FVC, a poor test performance usually leads to a falsely low value. On the other hand, an excessively slow start of exhalation, with a large back-extrapolated volume, may result in a falsely high FEV_1 .

There are some technical problems in obtaining valid MEFV curves. Apparatus must be capable of measuring both flow and volume with fidelity. The MEFV display requires X-Y recording; standard X-Y recorders are generally too slow to respond satisfactorily to on-line signals unless these signals are markedly attenuated. Curves may be photographed from an oscilloscope screen, stored on magnetic tape for subsequent computer processing, or held in temporary storage and given to the recorder at a reduced rate. This raises the cost considerably above that of timed spirometry. Also, it has not yet been demonstrated that V_{max} values are independent of measurement techniques.

The Closing Volume and Slope of Phase III

The closing volume (CV) is the point in exhalation at which basal airways are believed to close. An increased closing volume is regarded by some as a sensitive indicator of airways disease. Certainly, it does reveal abnormalities in smokers even when spirometric tests are normal. It may be measured either by inhaling a bolus of an inert gas such as helium (18), or by the so-called "resident nitrogen" technique (2). The latter technique is more popular because of its relative simplicity and because it provides an index of alveolar gas uniformity as well as a CV measurement.

To perform the resident nitrogen test, the subject exhales fully, takes a maximum inhalation of oxygen, and exhales slowly and steadily back to residual volume. Specific recommendations in regard to methodology have been published (30). The type of data obtained is shown in Figure I-20. The closing volume is usually expressed as a fraction of the vital capacity (VC). If the residual volume (RV) is known, a "closing capacity" (CC) can be calculated. This is simply the sum of RV and CV; it is usually expressed as a fraction of the total lung capacity (CC/TLC).

Unfortunately, the measurement of CV is invalid unless the subject exhales fully both be-

fore the inhalation of oxygen and on the subsequent slow expiration. Exhaling to the same point on both occasions and/or sustaining a slow, steady exhalation is difficult for some subjects. For these reasons, many technically unsatisfactory tests occur in field studies.

The test requires more expensive and sophisticated equipment than simple spirometry. Determination of the inflection point which marks the CV is subjective and not readily amenable to automation, leading to possible observer variation and even bias. The test shows wide inter-subject variation even when age and sex are taken into account, with reported standard estimate errors as high as 50% of predicted values (21). The significance of an abnormal CV remains unclear. On the other hand, the CV is occasionally normal even when there is frank spirometric abnormality.

The slope of phase III (Slope III), which can be measured from data obtained during the resident nitrogen technique (Figure I-20), may be a more useful indicator of functional abnormality than the CV measurement itself. It provides an index of alveolar gas uniformity, thereby detecting nonuniform function throughout the lung. Theoretically, it should be less susceptible to poor test performance or to observer error than the CV. It should also be relatively independent of such factors as chest size and thoracic muscle function—factors which probably increase the variability of spirometric measurements. The test is a better discriminator of smokers and symptomatic subjects than the CV/VC or FEV_1 , despite the fact that it shows wide intersubject variability (21) and that its intrasubject variability is greater than any of the other tests discussed thus far (42).

Helium Response of the MEFV Curve

The helium response of the MEFV curve is supposedly a specific test of small airways function. It does appear capable of detecting abnormalities in the airways which do not lead to frank spirometric abnormalities (13). The test is based on the fact that helium is less dense but at least as viscous as nitrogen. Replacing nitrogen with helium improves flow characteristics when flow is turbulent, but not when flow is laminar. When the lung is near full inflation, the maximum flow which can be generated (V_{max}) is limited by the large airways where flow is turbulent. As lung

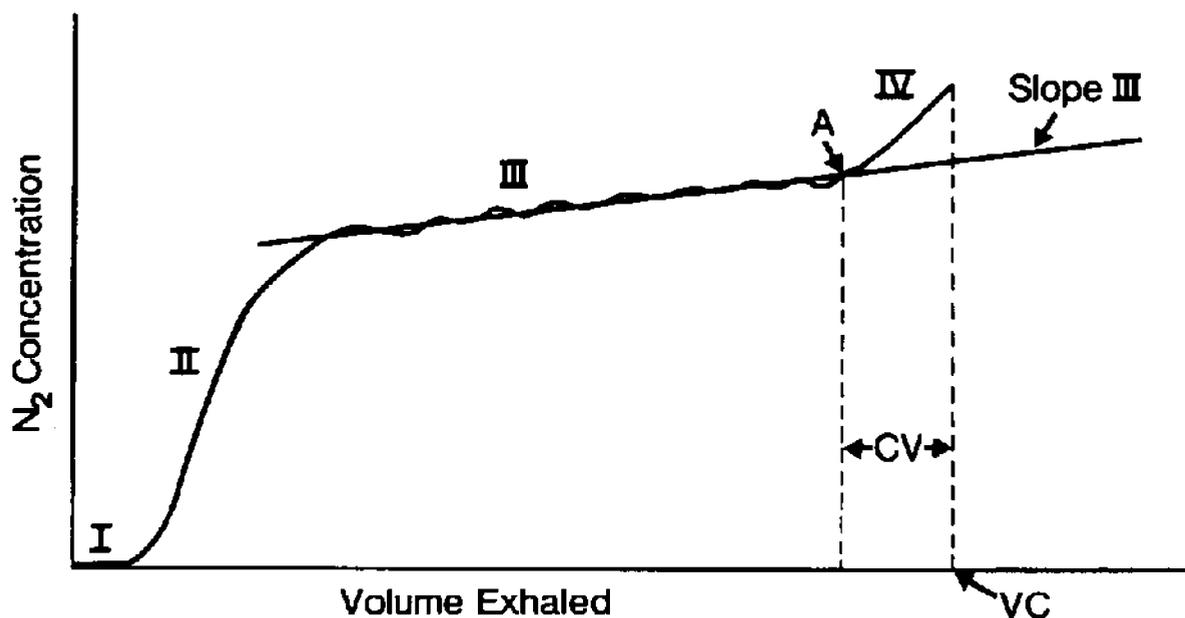


Figure I-20. Data obtained in a resident nitrogen closing volume test. The first gas exhaled (Phase I) is from the anatomic dead space which contains the pure oxygen previously inhaled. This is followed by a rapid rise in exhaled N_2 (Phase II) as alveolar gas begins to appear. A relative plateau of N_2 concentration then occurs (Phase III) reflecting a relatively constant alveolar air composition. Toward the end of the curve, a sudden upward deflection may occur (Point A) reflecting closing of basal airways. The closing volume (CV) is the amount of air exhaled following this inflection point (Phase IV) and is usually expressed as a fraction of the total gas exhaled (the CV/VC ratio). The slope of Phase III (Slope III) can also be measured by drawing a visually fit line through the relative plateau of N_2 concentration noted during that phase of the test.

volume decreases, the small airways, where flow is laminar, become increasingly important in terms of airways resistance and flow limitation. Normally, when one repeats the MEFV curve obtained on air after a subject has breathed a mixture of 80% helium and 20% oxygen, \dot{V}_{max} is markedly increased early in forced expiration. But post-helium \dot{V}_{max} tends to become similar to the air value as one approaches residual volume (Figure I-21). If there is disease of the small airways, the point at which helium fails to improve flow (the volume of iso-flow) occurs at a higher than normal lung volume, and the increase in flow after 50% of the FVC has been exhaled ($\Delta\dot{V}_{max}$ 50%) is less than normal.

While this test has certain theoretical attractions and probably can detect small airways abnormalities at an early stage, its applicability to epidemiological surveys has not been adequately evaluated. Certain features of the test make it less than ideal for field studies. Unless subjects are able to (almost exactly) reproduce their air FVC after breathing helium, measurements of the volume of iso-flow and of the $\Delta\dot{V}_{max}$ 50%

are unreliable. This problem results in a large number of technically unsatisfactory tests. Measuring the volume of iso-flow depends on determining the point at which two converging lines meet and is subject to considerable observer error. Intrasubject variability of the test has not been adequately studied; intersubject variability in a field situation has not been tested.

As originally described, the test was carried out with the subject in a body plethysmograph (13). The volume axis was measured plethysmographically, thereby accounting for any gas compression in the thorax which occurred during forced exhalation. The apparatus needed to perform the test in this way is cumbersome and the technology relatively complex. Although both flow and volume can be measured with spirometric type apparatus, this fails to account for differences in gas compression during the air test compared with the helium-oxygen test, which possibly changes normal limits and affects the maneuver's reproducibility. The helium response of the MEFV curve needs further methodological research before it can be recommended for

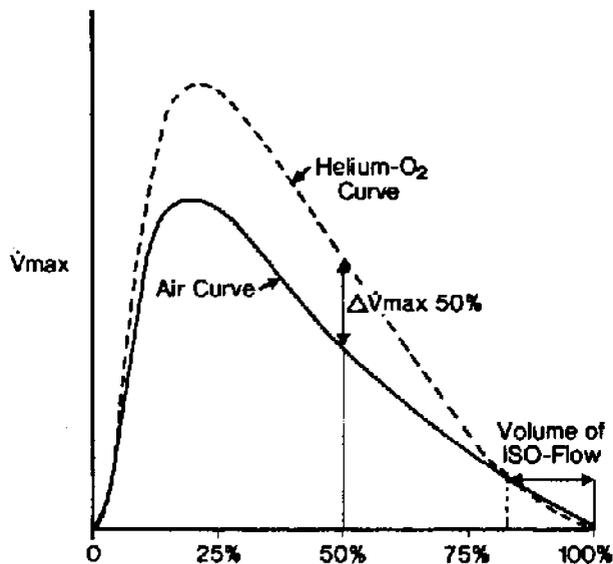


Figure 1-21. Data obtained during a test of the helium response of the MEFV curve. The MEFV curve obtained on air breathing is shown as a solid line; that obtained after equilibrating with a He-O₂ mixture as a broken line. The improvement in flow after exhaling 50% of the FVC ($\dot{V}_{\text{max 50\%}}$) can be measured and is usually expressed as a fraction of the air $\dot{V}_{\text{max 50\%}}$. Also, the gas exhaled following the point at which air and He-O₂ \dot{V} values become identical is sometimes measured and is called the volume of iso-flow. It is generally expressed as a fraction of the FVC.

survey use. It may, however, be of considerable importance in detailed evaluations which attempt to localize the site of disease.

Other "Sensitive" Tests

Measurement of frequency dependence of compliance is sensitive to nonuniform airways abnormalities, but it requires use of an esophageal balloon and is technically difficult (44). The test is totally unsuited to survey work and probably has few applications of any type at the present time.

Inert gas washout or equilibration curves, while theoretically capable of revealing subtle function changes, are seldom used in epidemiological studies. They are time consuming, require considerable subject cooperation, and have technical problems as well as an uncertain range of normal.

The Maximum Voluntary Ventilation

The maximum voluntary ventilation (MVV) is the volume of air breathed per minute with a maximum voluntary effort. This test has been

used extensively in clinical laboratories and is still favored by some clinicians as a guide to the overall function of the ventilatory pump. However, it requires considerable effort by the patient and is affected by the technician's coaching. Results depend to some extent on the instrumentation used and on the breathing pattern adopted by the subject. Furthermore, a properly performed MVV is closely correlated with the FEV₁. Indeed, an "indirect" MVV has been calculated in the past by multiplying the FEV₁ by a constant value (14). In view of the problems with the test and the fact that it provides no unique information about the physiological state of the lungs, it has little place in studies of occupational lung diseases except, perhaps, in disability evaluations.

Pulmonary Diffusing Capacity and Lung Volume Measurements

When occupational exposure is thought to produce a diffuse interstitial lung disease, measurement of pulmonary diffusing capacity should be considered as an addition to timed spirometry. Nearly a fifth of subjects with interstitial disease, who have normal spirometric tests, are classified as having abnormal diffusing capacities (14). Various methods for measuring diffusing capacity have been introduced. Steady state methods are technically difficult; may need to be carried out during exercise; and show great inter- and intrasubject variability. The single breath carbon monoxide method (Dsb), is more suited to epidemiological studies and has been recommended for investigations of interstitial diseases (14).

The Dsb requires a subject to exhale fully and then breathe in a mixture of approximately 0.3% carbon monoxide, 10% helium, 21% oxygen, and the remainder nitrogen. The breath is held at full inflation for 9 to 11 seconds, after which the patient exhales. The first 500 to 1,000 ml of the expirate is discarded. The remainder is collected and analyzed for helium and carbon monoxide. From a recording of the ventilatory maneuvers, knowledge of the inspired gas concentrations, and measurements on the expired gas, Dsb can be calculated—provided the volume of the lung during breath holding is known. The procedure can be automated, simplifying its use in field situations (16).

Most working subjects are able to cooperate well enough to exhale a sufficient volume of the gas mixture so that Dsb measurements can be

made. The test requires only moderate subject cooperation, and the duplicate measurements needed can be obtained within 15 minutes. Under ideal conditions, the intrasubject coefficient of variation on successive tests can be brought below 5% (14). However, this requires scrupulous attention to equipment calibration and proper test performance. Standardized procedures for the Dsb test have been published (14). Regardless of techniques, there is wide intersubject variability even when age, sex, and body size are taken into account; "normal limits" for the test are not well established.

As already noted, calculation of Dsb requires an estimate of the lung volume (V_L) during breath holding. The simplest method for calculating V_L is from the dilution of helium observed in the course of the Dsb test. This method appears as satisfactory as any for studies of subjects with normal lungs, with interstitial lung disease, or even with mild airways obstruction (14). In severe airways obstruction, this method may underestimate both V_L and Dsb.

To obtain accurate Dsb, total lung capacity (TLC), and residual volume (RV) measurements in subjects with severe airways obstruction, the plethysmographic method for determining thoracic gas volume is recommended (14). Standardized techniques have been described (27). It is uncertain, however, what place the test has in epidemiological studies. Although the RV and RV/TLC would be expected to be elevated relatively early in obstructive disorders, these measurements show so much intra-subject variability over time that they are not recommended for epidemiological investigations (42). And although the test is relatively quick and simple to perform, body plethysmography requires cumbersome and expensive apparatus and considerable technical expertise.

There are alternative methods for measuring lung volume, including nitrogen washout and inert gas rebreathing techniques (14). These methods are time consuming, require considerable subject cooperation, and are more suited to clinical than to epidemiological studies. Lung volume may also be estimated from the nitrogen dilution noted during the resident nitrogen closing volume test (4). While all these methods can be used for studies of subjects without severe airways obstruction (14), none have the reliability of body plethysmography. Radiographic measurements are a reasonable alternative to plethys-

mography when a chest radiograph is being obtained for other reasons (14). If radiographs are to be used for lung volume calculations, however, subjects must be at full lung inflation when the films are taken.

INTERPRETATION

Determining Normal Limits

Most pulmonary function tests show wide intersubject variability which is in part related to sex, age, body size, and race. These factors must be taken into account before attempting to interpret a test result.

One method of reducing variability is to calculate the ratio of two measurements which normally bear a relatively fixed relationship to one another. Common examples include the FEV₁/FVC, CV/VC, and RV/TLC ratios. A somewhat similar type of size correction is made when \dot{V}_{max} is measured at a fraction of the obtained FVC rather than after some absolute expired volume. While relating two measurements reduces the range of values and the coefficient of variation, it does not necessarily fully account for sex, age, or even body size relationships. Ratios also fail to reveal proportional changes in the two values being considered.

Another method of reducing variability is to adjust obtained values to a standard age and a standard body size. This technique is especially useful when comparing groups of subjects in a research report. In other settings, sex, age, and body size are usually accounted for by expressing data as a percent of some predicted value. Formulae to calculate predicted values are determined by multiple regression techniques applied to data from some reference population. Ideally, a presumed healthy subset of the population actually under study should be used. In a general population sample, the reference population might consist of subjects who have no respiratory complaints or known lung disease and who have never smoked cigarettes. When using such presumed healthy individuals, the apparent effects of age, sex, body size, and race—independent of disease—are evident from the prediction equations, and deviations from predicted in groups of subjects can be assumed to reflect their degree of abnormality.

Some of the more commonly used prediction formulae derived in this way for the FEV₁ and FVC are shown in Table 1-61. Three are

based on findings in asymptomatic nonsmokers in general population samples (9)(22)(31). Some asymptomatic smokers or ex-smokers were included in other studies. In one study, subjects aged 15 to 20 were included in the reference population (9). It is now known that FEV₁ and FVC increase with age in this group before beginning an age dependent decline (22). Inclusion of teenagers may have led to the relatively slight (apparent) age effect in the study of Cherniack and Raber (9). Most other studies show that in men over age 25, there is a fall in FEV₁ of approximately 25 to 30 ml per year and a fall in FVC of about 20 to 25 ml. For women over age 20, both values appear to decline somewhat less rapidly, but they are similar to those of males when considered as fractional declines.

Relatively few prediction formulae have been published for the FEV₁/FVC ratio. It has been common practice to calculate the predicted ratio as 100 x Predicted FEV₁/Predicted FVC. Certainly, the ratio does show a decline with age. While it generally exceeds 80% up to the age of 55, mean values fall as low as 70% to 75% after age 60 (38). In order to more validly predict the FEV₁/FVC ratio, investigators should probably use the actual value obtained from the reference population of observed FEV₁ divided by observed FVC for each subject, and develop a regression equation in the same way as has been done for the predicted FEV₁ and the predicted FVC. Recently published prediction formulae for this ratio expressed as percent are as follows:*(22)

Males: 103.6—0.14 Age—0.087 Ht (cm)

Females: 107.4—0.11 Age—0.11 Ht (cm)

These predictions are all based on cross-sectional analyses. They may be useful for predicting values within the existing population, but because of cohort effects, they do not necessarily indicate longitudinal changes. It is possible that individual age changes in function are less in magnitude and more nonlinear than those found in cross-sectional studies.

Occasionally, the total study sample is used to predict lung function levels. One must then be cautious in interpreting percent predicted values, especially if a large proportion of the population may be at risk for a pulmonary

*The relationship to height is of interest, and suggests that large subjects, expected to have large FVC's, tend to get out a smaller fraction of their total volume during the first second of exhalation.

disorder. For example, the cumulative effects of smoking in a general population sample would increase the apparent effect of age and lead to a large standard error of the estimate (SEE). When predictions are based on the entire study group, healthy individuals will show mean percent predicted values greater than 100% while deviations from predicted will be minimized in affected subjects. In this situation, effects of exposure to a suspected noxious agent must be evaluated by comparing percent predicted findings in exposed and nonexposed subjects. "Predicted" cannot be equated with "healthy" if the reference population includes presumed unhealthy subjects.

When there are too few subjects to allow age, sex, and body size regressions in the study group itself, prediction equations derived from some other population must be used. However, prediction formulae are *never* strictly applicable to any population other than the one from which they were derived. Differences in race, ethnic background, socioeconomic conditions, time of study, test technique, subject motivation, and a myriad of other factors can affect predicted levels. If one must use prediction formulae derived from another reference population, that population should resemble the one under study as closely as possible, and only comparisons between different groups within the study sample are meaningful. Absolute deviations from predicted can be misleading. A recent report by Lanese noted several studies confirming "normal" black subjects have significantly lower FVC and FEV₁ values than whites—even when age, sex, and height are taken into account (24). It has been recommended that values predicted for these measurements derived from predominantly or wholly white populations (see Table I-61) be reduced by 13.2% when applied to blacks (11)(37). Since the forced vital capacity ranges 10% to 15% lower for blacks (1), this recommendation appears reasonable until better race specific prediction formulae are developed. The FEV₁/FVC ratio shows less difference between blacks and whites and probably does not require an adjustment for race, although it may be slightly higher in black than in white men.

When comparing results of different lung function tests, predicted values for all tests must be derived from the same reference population.

Table I-61
PREDICTION FORMULAE

A. For FEV₁ (liters)

	Coefficients		Constant	Reference
	Age (Years)	Standing Ht. (cm)		
Males	-.028	.037	-1.93	(23)
	-.032	.036	-1.26	(31)
	-.023	.036	-1.507	(9)
	-.031	.033	-0.897	(38)
	-.027	.052	-4.203	(22)
Females	-.021	.028	-0.87	(40)
	-.025	.035	-1.932	(31)
	-.019	.024	-0.187	(9)
	-.027	.026	-0.525	(38)
	-.021	.027	-0.794	(22)

B. For FVC (liters)

Males	-.022	.052	-3.60	(23)
	-.025	.058	-4.24	(31)
	-.014	.048	-3.18	(9)
	-.022	.047	-2.82	(38)
	-.029	.065	-5.46	(22)
Females	-.018	.041	-2.69	(40)
	-.024	.045	-2.85	(31)
	-.015	.031	-1.05	(9)
	-.022	.037	-1.92	(38)
	-.022	.037	-1.77	(22)

NOTE: All reference populations were restricted to whites except for that of Smith and Kory (40).

If a new test's predicted values are derived from a "healthier" group than predictions from established tests, the new test will invariably appear to be a more sensitive disease detector.

Having taken into account the effects of sex, age, body size, and race by relating findings to a predicted value, it may be important to determine whether a percent predicted or adjusted value for an individual is "within normal limits." Limits of normal for lung function tests are totally arbitrary. If prediction formulae are derived from the total population being studied and normal limits based on deviations around predicted data, the number of "abnormalities" in the total sample will be predetermined. When predicted values are derived from presumed healthy subjects in the sample, the same procedure results in a predetermined number of abnormalities in that reference group. The number of "abnormal" tests in the total sample will then

depend on the difference in values obtained in other subjects compared to those in the reference group. The more carefully screened the reference population, the more "abnormalities" will be found in the remainder of the sample.

When obtained data in the reference population are distributed in a Gaussian fashion around predicted data, "normal limits" are usually set on the basis of the SEE of the prediction equation. For values reduced by disease (such as the FEV₁), setting normal limits at 2 SEE below predicted will result in approximately 2.5% abnormalities in the reference group. If one is willing to accept a higher rate of abnormalities in that group, limits of "normal" can be set at 1.64 SEE below predicted, giving an approximate abnormality rate of 5%. This assumes that the SEE is independent of the predicted level. In fact, the SEE may be approximately proportional to the predicted value, and

in this case, "normal limits" are more appropriately expressed as a percent of predicted.

Deviations from predicted do not always follow a Gaussian distribution. For example, the $\dot{V}_{max} 25\%$ tends to show marked skewness toward above predicted values. If "normal limits" are set at 2 SEE below predicted, zero may appear to fall within the "normal range" (22). Either the data must be transformed (perhaps made into a logarithmic function) or "normal limits" must be set by some method which does not assume a known distribution pattern. If numbers allow, one may simply examine obtained data to find the level at which a given fraction of the reference population is arbitrarily classified as abnormal. This technique has the advantage of fixing quite precisely the number of apparent abnormalities in the reference population. It has been used effectively when examining the relative ability of different tests to detect excess abnormalities in smokers or symptomatic subjects (19).

Regardless of the specific method used to set "normal limits," they should not be interpreted as separating health from disease. Even within the normal range there will be an increasing probability that disease exists as one progresses from above predicted to low-normal values. In research studies, enumeration of "abnormalities" in population groups should be regarded only as an illustrative procedure. Determining that a functional test is different in one group than another requires examination of the overall distribution of values in the two groups.

When it is necessary to decide whether an individual lung function test is "normal" or not, the following procedure may be used. If the test is more than 2 SEE below predicted, it is generally presumed to be "abnormal," provided the low value is confirmed on retesting. When the measurement being examined falls in the range of 1.64 to 2 SEE below predicted, a second measurement may be examined. In the case of a borderline percent predicted $FEV_{1,}$ for example, the $FEV_{1,}/FVC$ ratio or $FEF_{25-75\%}$ can be examined. If the second test is also more than 1.64 SEE below predicted, it is reasonable to assume disease is present. On the other hand, it is inappropriate to use an abnormality in any one of multiple measurements as an indication of abnormal lung function. As more tests are considered, more subjects in the reference population will show at least one "abnormal" measure-

ment. This is true even when measurements are closely related, as in the case of multiple indices of forced expiratory flow (19).

There are more scientifically defensible ways to express the extent to which a lung function test resembles measurements found in a reference population than by calling it "normal" or "abnormal." The actual number of SEE's by which the value differs from predicted gives an index of the likelihood of finding such a value in the reference population. One may also readily convert the SEE information into probability figures. Thus, a value which is 1.3 SEE below predicted can be interpreted as follows: "This low a value is found in approximately 10% of asymptomatic nonsmokers in the population."

Assessing the possible effects of other exposures in cigarette smokers is a complex problem. Clearly, even asymptomatic current or ex-smokers show lower lung function values than nonsmokers and the effect appears to be related both to intensity and duration of cigarette use (7). While published data might allow an adjustment for smoking, the adjustment's reliability would be uncertain. The range of "normal" in smokers has not been, and perhaps cannot be, determined with precision.

Finally, it should be remembered that prediction equations are derived from a selected portion of some general population—usually asymptomatic nonsmokers. No unscreened population would be expected to have this level of function. Even if smoking habits are taken into account, almost any unscreened population, even if not exposed to noxious agents, will contain some portion of symptomatic subjects whose lung function is impaired. Thus the fact that some unscreened industrial population has average lung function values below predicted does not necessarily indicate that it is different from any other general population sample.

Patterns of Abnormalities

Airways obstructive disorders are characterized by a reduction in forced expiratory flow which is out of proportion to any reduction in the total volume of gas exhaled, and leads to a low $FEV_{1,}/FVC$ ratio. There is also an increased RV and a high RV/TLC ratio. This is the pattern of "obstructive lung disease" and is characteristic of asthma, emphysema, and chronic obstructive bronchitis. Other physiological findings in these diseases depend on the anatomi-

cal abnormalities underlying the airways obstructive problem as well as on the stage of the disease (6). With advanced anatomic emphysema, the TLC is large, pulmonary diffusing capacity markedly reduced, lung recoil very low, and resistance of the large airways (measured by body plethysmography) near normal. There may be relatively mild hypoxemia and no elevation of the arterial carbon dioxide tension until late in the disease. Patients with this type of disorder have been called "Type A" or the "emphysematous type" of chronic obstructive lung disease, or "pink puffers." In contrast, patients with minimal emphysema, but severe intrinsic disease of the airways, show less pulmonary hyperinflation, less consistent reduction of diffusing capacity, little loss of lung recoil, and high airways resistance measurements. They tend to have severe hypoxemia, chronic hypercapnia, and cor pulmonale relatively early in their disease. Such patients have been called "blue bloaters," or characterized as "Type B" or as a "bronchial type" of chronic obstructive lung disease. In fact, these distinctions are quite artificial. Classical examples of either type of disease are relatively rare since most subjects with chronic irreversible airways obstruction have both emphysema and intrinsic airways disease.

Asthma can be distinguished from chronic irreversible airways obstructive disorders only by the reversibility of the physiological abnormalities. The improvement which occurs within minutes of inhaling a potent beta adrenergic bronchodilator should be observed. When an obstructive abnormality is markedly improved by bronchodilator inhalation, some asthma must have been present. However, many severe asthmatics prove refractory to a single dose of inhaled medication. The reversibility of their abnormality may be seen only after a prolonged program of medical management. Thus, the type of testing which is usually done in field situations does not permit differentiation of asthma from irreversible airways obstructive diseases.

Special care must be taken in assessing acute changes in lung function after bronchodilator inhalation or with challenge tests. The total FVC as well as flow rates may change. Thus, alterations may be missed if the FEV_1/FVC ratio is examined. Also, \dot{V}_{max} values can be misleading unless they are examined at the same absolute volume of exhalation (29).

It has been recently reported that subjects with late onset "intrinsic" asthma are more likely to show diminished response of the MEFV curve to helium/oxygen inhalation than are "extrinsic" asthmatics (3). This suggests that the problem in "intrinsic" disease is located in more peripheral airways. However, the reliability of the helium-oxygen test in distinguishing different types of asthma needs to be confirmed.

A different pattern of abnormalities is noted in subjects whose airways are not obstructed, but whose lungs are less compliant than normal because of inflammatory changes or fibrosis. Here, the vital capacity, FVC, and TLC are reduced, but expiratory flow rates are relatively unimpaired. Thus, the FEV_1/FVC ratio is not decreased. This pattern of "restrictive lung disease" is totally nonspecific. It occurs with any disorder which limits inspiration—abnormalities of the chest wall, any type of parenchymal lung disease except emphysema, and even poor patient effort. When it is the result of diffuse interstitial disease, additional abnormalities often occur, including a marked reduction in diffusing capacity and increased lung stiffness noted on pressure-volume studies. There may also be arterial hypoxemia which is made worse by exertion, corrected by small supplements of oxygen, and accompanied by a normal or even low arterial carbon dioxide. This constellation of findings has been called an "alveolar-capillary block syndrome." While doubt has been expressed that a true alveolar-capillary block exists in most patients, the described pattern of abnormalities is characteristic of diffuse interstitial lung diseases.

When only spirometric data are available and TLC is not known, interpretation is limited. If the FEV_1 is reduced out of proportion to the FVC, producing a low FEV_1/FVC ratio, "obstructive ventilatory impairment" can be said to exist. If the FVC or VC is below normal limits, but the FEV_1/FVC ratio is not reduced, a "restrictive ventilatory impairment" is present.

There are many diseases which produce both a small lung as well as a problem with airflow. In this case, both the FEV_1/FVC ratio and the total lung capacity are reduced, and a "mixed" type of abnormality is present. All in all, pulmonary function tests are of limited value in diagnosis beyond distinguishing diseases which primarily affect airways function from those

which increase the stiffness of the lung and therefore decrease its distensibility.

THE MEANING OF PULMONARY FUNCTION ABNORMALITIES

The relationship of lung function tests to symptoms and prognosis in patients with severe irreversible airways obstruction is reasonably well documented. In these patients, the FEV₁ shows a crude but definite relationship to the severity of clinical illness. For example, most patients note dyspnea only on moderate exertion when their FEV₁ exceeds 1.25 liters, even though this value is less than half of predicted. Dyspnea on slight exertion and complications of the disease are seen more frequently as the FEV₁ falls below 1.0 liters. Complete invalidism generally occurs as the FEV₁ approaches .5 liters. Survival shows a relationship to a great variety of lung volume measurements, but is best correlated with FEV₁ obtained after bronchodilator inhalation (43). The median survival is less than three years when the FEV₁ is below 30%, approaches five years when the FEV₁ is in the range of 30% to 40%, and is near ten years when the FEV₁ is close to 50% of predicted. While there are wide variations around these median survivals, a lung function test does provide a crude index of a disease's stage.

In asthma, fluctuating symptom severity is reasonably well reflected by changes in the FEV₁, but longevity has not been studied in relationship to function tests. There is some correlation between vital capacity and survival in patients with idiopathic diffuse interstitial fibrosis, but the relationship is not close. Evidence relating symptom severity or survival to lung function measurements are lacking for most other diseases, but nearly all clinicians would agree that severe blood gas or spirometric abnormalities are poor prognostic signs in any progressive respiratory insufficiency state.

Work status has been shown to have some relationship to measured functional impairment in patients with chronic airways obstruction who are not applying for disability benefits (12). Most subjects continue to work at sedentary jobs until their FEV₁ falls below a liter. Work status is also related to certain psychological factors (10); in disability applicants, there appears to be little correlation between measured impairment and self-perceived disability (28).

It is important to remember that pulmonary

function tests do not necessarily measure the specific functional characteristics which lead to symptoms. Indeed, the actual mechanism of dyspnea remains unclear. Thus, although function tests are useful for confirming the presence of disease, for following its course, and sometimes for determining the type of anatomical abnormality present, such tests cannot measure the total impact of the disease. Also, disease progression rates are generally variable, and lung function studies can be expected to produce only crude estimates of longevity.

It has become popular to use lung function tests for "early detection" of chronic airways obstructive diseases. This is based on the theory that these diseases develop slowly and gradually throughout adult life, and that the subject who will have severe airways obstruction at age 60 should show a mild subclinical impairment of lung function by age 40 or 45. It has been shown that middle-aged subjects with mildly diminished FEV₁'s do tend to have relatively rapid declines in lung function over a period of several years. The decrements in lung function of subjects with lower test values have been described as the "horse-race effect" (15). However, there is wide variability in reported data and the precision with which spirometric test can detect the individual who will later develop incapacitating disease remains unclear.

The use of more sensitive tests to detect "early" disease is problematical. V_{max} 25%, slope of Phase III, and closing volume detect more abnormalities in smokers than the FEV₁ (21)(22). However, the significance of such abnormalities is uncertain. It is not known if they are predictive of later development of progressive disabling illness; it is not even known if they persist within individuals. According to the "horse-race effect," a good FEV₁ in middle-age should preclude succeeding severe disease regardless of findings on more sensitive tests. At our present state of knowledge, isolated abnormalities in V_{max} 25%, slope III, closing volume, or helium/oxygen response of the MEFV curve are best regarded as indicative of mild lung dysfunction but not necessarily of an "early" stage of a progressive disease.

When an abnormality is found in a more clinically relevant measurement such as the FEV₁, the abnormality should be confirmed and its irreversibility demonstrated. Response to inhalation of an adrenergic bronchodilator should be

observed. A high proportion of mildly abnormal tests, detected in a population survey, increased to "within normal limits" after isoproteranol inhalation (29). An FEV₁ persistently below 60% of predicted is generally associated with some clinically significant symptoms; in the presence of a low FEV₁/FVC ratio, it is compatible with frank airways obstructive disease. A persistently low FEV₁ (i.e., 60% to 75% of predicted) indicates a subject at high risk of later developing more severe ventilatory impairment, but the magnitude of this risk remains to be determined.

Assessing Severity of Abnormality

There tends to be confusion between the clinical and statistical significances of a test abnormality. The CV/VC may be several SEE above predicted, and therefore, "definitely abnormal" in a statistical sense. However, this hardly indicates a "severe abnormality" in clinical terms. The clinical importance of an isolated abnormality in CV/VC remains unclear. To avoid confusion, it might be reasonable to accept certain conventions. When referring to the statistical confidence of abnormality, tests might be classified as normal, low normal, borderline, or definitely abnormal. Terms such as mild, moderate, and severe abnormality are probably best restricted to assessments of clinical significance. This can only be determined by empiric observations relating symptoms and prognosis to test results.

Possible guidelines for expressing the relationship of a test to findings in a reference population, using terms understandable to most clinicians, are shown in Table I-62. For the FEV₁, FVC (or VC), and blood gases, a clinical appraisal may also be provided based on empiric observations, but this is possible for few other tests. In clinical terms, an FEV₁ in the range of 60% to 75% of predicted might be considered a mild abnormality, whereas tests in the ranges of 45% to 60%, 30% to 45%, and less than 30% might be considered moderate, severe, and very severe abnormalities respectively. The FEF_{25-75%} tends to stabilize in late stages of disease. It is therefore less satisfactory than the FEV₁ for assessing either the stage or course of an airways obstructive disease. The same must be true of V_{max} values, slope III, and even the FEV₁/FVC ratio (5).

CHALLENGE TESTING

Challenge tests have been used for two distinct purposes. The first is to evaluate the general state of bronchial reactivity. For this purpose, inhaled histamine or methacholine may be used, or the response to vigorous exercise may be observed. A standardized protocol must be followed to obtain meaningful results (8). Most asthmatics show falls in lung function after inhaling much smaller doses of histamine or methacholine than are required to affect the lung function of normal subjects. Similarly, most asthmatics show excessive fluctuation in lung function during severe exercise. Intermediate responses noted in patients with allergic rhinitis and relatives of asthmatics are presumed to indicate a milder degree of bronchial hyperreactivity than is seen in overt asthma (17). Such challenge tests have been used to confirm the diagnosis of asthma during remissions of illness. They are of substantial research interest because of their potential to identify the individual who will be most affected by exposure to a bronchial irritant or allergen, but this has not yet been documented.

Table I-62

RELATIONSHIP OF RESULTS TO A REFERENCE POPULATION

Number of SEE from Predicted*	Interpretation
<1	Normal
1—1.64	Low normal range
1.64—2	Borderline abnormality
<2	Definite abnormality

*Based on findings in an asymptomatic, nonsmoking general population sample.

It is technically possible to use histamine and methacholine challenges in the field. Theoretically, these tests might even be applied to large population groups. There are certain problems, however. Considerable patient cooperation is required. The tests are time consuming and require a physician's attendance. Also, there is a risk of inducing a first asthmatic attack in a predisposed subject. Were this to happen, the subject might interpret the test as a cause of his disease. Unfortunately, exercise testing is not practical for field use. Vigorous exercise is required, and many subjects cannot complete

the protocol.

The second use of provocative testing is to confirm that a specific inhalant provokes symptoms and physiological abnormalities. This is most often used to identify factors leading to acute bronchospasm (8) but has also been used in regard to hypersensitivity pneumonitis (34). This type of testing is totally unsuited to large scale studies and should only be carried out under an experienced physician's direct supervision.

While as crude a measure as peak flow (measured with a Wight Peak Flow Meter) has been effectively used in assessing exercise responses (17), airways resistance measured in a body plethysmograph is more sensitive to acute bronchospastic changes than measurements from the timed spirogram or the MEFV curve. When using this technique, subjects must be exposed to an inert material as well as the suspected noxious agent in a blind fashion since placebo effects do occur, and mild bronchospasm may be induced by suggestion (41).

Even without a formal challenge test, the acute effects of a suspected provocative factor may be studied by checking lung function studies before and after a subject is naturally exposed. This technique has been used to determine whether exposure to air pollutants affects the lung function of exercising school children (26). It has also been widely used to see if occupational exposures cause lung function to decline over the course of a work shift, or when a subject returns to work after an absence of several days (32). A fall in the FEV₁ of greater than 15% is generally considered indicative of significant bronchospasm.

Some investigators consider it important for overall quantitative accuracy that tests be performed at the same time of day and same season of the year, especially if workers are to be monitored for longitudinal studies. Whether the use of pulmonary function tests in shift studies and air pollution detection effects ought to include this aspect of seasonal and diurnal variability is debatable because (1) the variability is usually so small as to be statistically insignificant and (2) scheduling tests pursuant to this possible variability is only sporadically feasible.

Research Needs

Research needs in the application of pulmonary tests to occupational disease studies include:

1. Determination of simple, accurate prediction formulae for commonly used pulmonary tests for nonwhites.
2. Investigation of the prognostic significance of "sensitive" tests of lung function, including instantaneous flow measurements toward the end of the flow-volume curve, closing volume and Slope III measurements, and the response of the flow-volume curve to helium inhalation.
3. Determination of the usefulness of tests of bronchial reactivity (bronchial challenge test) in identifying workers who may be especially sensitive to occupational exposures.
4. Investigation of the relationship of "shift changes" to longitudinal changes" in lung function.
5. Improvement in our ability to distinguish smoking effects from those of occupational exposures. At a minimum, this would require more accurate prediction equations for smokers with varying smoking habits and varying pack-years of cigarette use.
6. Improved statistical methods for dealing with longitudinal observations of lung function where the variability of measurements generally far exceeds the true annual decline.

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RESPIRATORY QUESTIONNAIRES

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INTRODUCTION

Well-designed questionnaires are an important and powerful tool in the exploration of occupational health problems and associated risk factors. They are easy to apply, inexpensive to administer, and readily interpretable.

Unfortunately, the apparent simplicity of the questionnaire technique is deceptive. There is much more to survey work than drafting a set of questions and applying them haphazardly to groups of individuals. The proper use of a questionnaire is dependent on careful design, subsequent verification of validity and reproducibility, and the close monitoring of its application. The careless use of questionnaires has been and continues to be a major source of erroneous results and conclusions.

DESIGN CONSIDERATIONS

In the course of ascertaining information by questioning groups of people, it was soon realized that the method of *free questioning*, as used in clinical situations, was inadequate. Van der Lende and Orié have said, "... in these procedures [free history taking], errors of omission can act inadvertently or deliberately, irregularly or consistently. The way the clinician asks the questions, the attitudes, the approaches, and the vocabulary may evoke incomplete, inaccurate, or evasive answers. Furthermore, a different opinion of the meaning of a symptom can be a source of error"(25). They go on to say, "obviously, with so many possibilities of making mistakes, *free* history taking, with 'open' questions is unsuitable for epidemiological purposes..." This was clearly demonstrated by Cochrane and others who used a fairly free form of questioning to inquire about certain symptoms such as cough and phlegm (5). They reported the method appeared to give rise to large differences between interviewers. These results spurred the development of a standardized ques-

tionnaire—the British Medical Research Council Questionnaire on Respiratory Symptoms (BMRC) (15)(16).

The first step to take after deciding to use a questionnaire is to list the disease processes which are to be investigated. If these are covered by an established questionnaire, it is probably better to use that version rather than drafting a new questionnaire, provided the existing format has been tested and verified for validity and repeatability. If it is necessary to draw up a new questionnaire, its content must be defined by enumeration of those items about which information is sought. Each item must be described in terms of its manifestations and translated into a list of questions. When deciding whether to include a question, Hill's dictum should be applied: "For every question the investigator wishes to include he should ask himself—'Is this question really necessary?'" This is especially important for questionnaires in occupational epidemiology where time is a factor that can affect response.

Once the investigator has chosen his questions, he must determine their specificity and sensitivity and select their form and wording. Specificity and sensitivity will be discussed later.

There are two forms of questions: open and closed. Open questions, where the respondent is required to answer freely with no constraints, are generally unsuitable for epidemiological purposes. Questions such as: "Have you received any medical treatment in the past year?" result in answers that pose enormous problems in data processing and analysis. They also rely on the respondent's memory; prompts, such as a list of diseases or illnesses, are not given to aid recall.

The closed question offers a fixed choice of responses. The simplest form requires a dichotomous response such as YES/NO. Other types offer a list of choices, one of which must be chosen. This list may show a gradient from

one extreme to the other. Another type offers a list where one or more of the elements can be checked and is especially useful because it provides prompts to aid the respondent's memory (e.g., a list of different chest illnesses). For further discussion on the design of questions and indeed on all aspects of medical questionnaires, see Bennett and Ritchie (3).

The wording of questions is a crucial aspect of questionnaire design. One defect is phrasing that suggests a particular answer. The leading question, such as "You do cough," is the most extreme example of this. Vagueness and ambiguity are faults often found in questionnaires. For example, Suchman et al., found that there was confusion as to what constituted "trouble" in the question, "Do you have trouble with your hearing?" (23). Phrasing that decisively inquires about a particular disease entity can be difficult to achieve. Although medical jargon has distinct meaning for physicians, the layman is frequently confused about what terms mean (Boyle)(4). Bennett and Ritchie argue that words implying frequency (such as "often" and "sometimes") should be replaced by more precise terms (3). In addition, it is best to avoid questions that require long recall such as, "Have you ever had . . ."; instead use specific time periods such as, "in the past three years" or "before age eighteen."

Questions should be as short and contain as few concepts as possible. For example, question five of the British Medical Council's questionnaire on respiratory symptoms asks, "Do you cough like this on most days for as much as three months in the year?" (16). This contains three major concepts: "cough like this"; "on most days"; and "for as much as three months in the year." Each concept requires three different memory recalls: one to remind him of the previous questions ("like this") and two to past events. He must also make a judgment concerning what constitutes "most days" and "for as much as three months in the year."

Some researchers believe that valid results can be attained if information on the cooperativeness of the respondent is available. For example, uncooperative respondents could be eliminated from analysis where there are grounds to believe their answers are untrustworthy. There are several ways of doing this. One method simply asks the interviewer to assess how cooperative the respondent is. Another method

elicits the information by inserting (into the questionnaire) questions for which there is a known correct response.

The final design consideration is question order and layout. A "carry-over" effect from preceding questions may influence answers to later ones. This can arise because the respondent strives to present a consistent picture of his symptoms to himself and the interviewer. Alternatively, earlier questions can remind him about aspects of his illness he may have forgotten. Thus in the BMRC questionnaire, the phlegm questions occur after those on cough. If a respondent associates phlegm with coughing but does not admit to cough, he will probably not admit to phlegm. If the position of the two sets of questions were reversed, perhaps more people would state they had phlegm without cough. (This possibility is stated explicitly on that questionnaire).

In laying out the questionnaire, it is important that instructions to the interviewer on question order and on skipping questions be stated clearly. Errors due to incorrect skipping have been reported by Attfield and Melville; these resulted from unclear instructions on the sheet (2). It may also be desirable to print instructions to the interviewer on answer interpretation, close to the relevant question rather than in a separate instruction book. Thus the wording, "most days," in the BMRC questionnaire could be clarified by the direction, "most days means five or more days per week," set in a note close to the question. In this way the interviewer would be constantly reminded. Finally, most questionnaire information is nowadays processed by computer. This involves the transfer of information to computer storage and this transfer can cause errors. It is imperative that the questionnaire sheet be organized for easy and accurate data coding and transfer. The advice of a computer programmer or systems analyst can be invaluable.

AN EXAMPLE OF A MEDICAL QUESTIONNAIRE

As an example of an established medical questionnaire, the British Medical Research Council's respiratory questionnaire is described and reviewed here (15). The development of this questionnaire was spurred by the results of several epidemiological studies, notably that of Cochrane and colleagues, which had revealed the inadequacies of free questioning in large studies

(5). The BMRC questionnaire was published in 1960 and revised in 1966 and 1976. As Samet has said, "The questions...reflect the hypothesis about the origins of airway obstruction which prevailed in the 1950's..."(21). The questionnaire has been used widely, translated into other languages, and often modified. In Europe it formed the basis for European Coal and Steel Community's investigations into respiratory disease (see Van der Lende and Orié (25)). A shortened version has been used by the Pneumoconioses Field Research of the British National Coal Board (for format see Attfield and Melville (21)), and clear associations between symptom levels and quantitative measures of dust exposure have been demonstrated (20).

In the United States a committee of the American Thoracic Society adopted the questionnaire in 1968 (1). In 1971, the National Heart and Lung Institute (NHLI) made available a version of the BMRC questionnaire, adapted for use in the United States (6). Recently a committee organized by the American Thoracic Society has released a recommended questionnaire named the ATSDLD-78-A; it is based on experience gained with the BMRC and NHLI questionnaires (9). This version has a similar format to its predecessors but differs from them mainly by inquiring about illnesses in childhood. It is more suitable for occupational epidemiology as it seeks to determine how long respondents have had symptoms and illnesses, thereby allowing the researcher to link symptoms and exposure more precisely.

Up to now, however, the BMRC version has been the most widely used questionnaire. The BMRC questionnaire asks questions on cough, phlegm, wheezing, breathlessness, chest illness, and other factors. It has comprehensive sections on smoking habits and on occupational history. Instructions on question order are clear and clarificatory notes are printed in the text. Layout and transfer to computer storage are uncomplicated. The validity and reproducibility have been tested and its utility verified by countless studies in which it has been used.

QUESTIONNAIRE VERIFICATION

Verification of a questionnaire involves two concepts: validity and reproducibility. These have been introduced and discussed in the section on Epidemiology and Study Design in this chapter. As mentioned there, reproducibility

measures the random variation seen on different occasions; a valid questionnaire is one in which results agree with the best possible measurements that can be made to determine the presence or absence of disease (or exposure).

VALIDITY

Validity can be divided into two concepts: sensitivity and specificity. Sensitivity is a measure of the proportion of truly diseased persons found to be positive for disease by the questionnaire or test procedure. The numerator of this index is the number of all true positives; the denominator is the sum of the true positives and false negatives (Table I-63). Table I-64 gives some data on men aged 40-64 in Vlaardigen, Holland, who were examined by the BMRC questionnaire and given a bottle in which to collect sputum over 24 hours. The 43% figure does not show high sensitivity, but the authors give valid reasons as to why that figure should be considered satisfactory.

Table I-63
CALCULATION OF SENSITIVITY

	Disease Present	Disease Absent
Positive replies	a	c
Negative replies	b	d

$$\text{Sensitivity} = \frac{a}{a + b} \times 100$$

Source: Historical Definition.

Table I-64
EXAMPLE OF SENSITIVITY CALCULATION

	Sputum Present	Sputum Absent
Yes to BMRC question 10	104	22
No to BMRC question 10	138	203

$$\text{Sensitivity} = \frac{104}{104 + 138} \times 100 = 43\%$$

Source: (25)

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The main problem with determining sensitivity is that the value of the index is dependent on the degree of similarity between the two measures being compared. In Table I-65, the two methods are not directly comparable: question 10 of the BMRC questionnaire is concerned with phlegm on most days for as much as three months in the year; the sputum samples were collected on one day only. Men who said "yes" validly to question 10 may not have been able to produce sputum on the one day they were given the bottle. Thus, although the question answer and the sputum collection apparently disagree, and cause the sensitivity index to be reduced, such disagreement is perfectly allowable. Unfortunately, when using questionnaires, it is seldom possible to devise an independent test which is reliable and which is *absolutely* comparable to the question. The result of this is to make sensitivity figures only approximate guides to true sensitivity.

That an index other than sensitivity is needed can be demonstrated in an example. Suppose, in a study of respiratory symptoms, we wish to include a question with great sensitivity to identification of bronchitis. One question which would certainly identify such people would be "Have you ever coughed?" While this has excellent sensitivity, it would also identify many of the nonbronchitics. In other words, it is not specific to bronchitis. In order to measure this effect we need another index. This index, *specificity*, is defined as the quotient of the number of truly nondiseased found to be negative by the questionnaire or test and the sum of true negatives and false positives (Table I-65). While sensitivity measures the ability of a questionnaire or test to discover a large proportion of the diseased persons subjected to examination, specificity measures the ability of the questionnaire or test to identify those truly nondiseased. Usually, the more sensitive a questionnaire is made, the lower its specificity tends to become. Table I-66 gives an example conceiving specificity, taken again from the Dutch study of Van der Lende and Orié (25).

Most studies in occupational epidemiology involve the effects of inhaling dusts or vapors and so include a respiratory symptoms questionnaire. It is in this field, therefore, where the investigation of sensitivity and specificity has been studied most. Even so, as Samet has noted, there are few appropriate standards with which

to assess the validity of questions on cough, phlegm, and dyspnea (21). In his review of the history of the respiratory symptoms questionnaire, Samet discusses the various attempts to validate questions. He notes that validation of the BMRC questionnaire has been limited to assessment of questions on phlegm, dyspnea, and chest illness, and comments that only the phlegm questions have been adequately validated. For these questions the sensitivity and specificity are good. For the rest, the findings are mixed but generally favorable, although assessment is dogged by the unavailability of a realistic standard.

Table I-65
CALCULATION OF SPECIFICITY

	Disease Present	Disease Absent
Positive replies	a	c
Negative replies	b	d

$$\text{Specificity} = \frac{d}{c + d} \times 100$$

Source: Historical Definition.

Table I-66
EXAMPLE OF SPECIFICITY CALCULATION

	Sputum Present	Sputum Absent
Yes to BMRC question 10	104	22
No to BMRC question 10	138	203

$$\text{Specificity} = \frac{203}{22 + 203} \times 100 = 90\%$$

Source: (25)

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REPRODUCIBILITY

Apart from validity, a questionnaire must be reliable; i.e., the random variation in the answering of questions must not be great. Reliability is measured by a statistic which is variously named consistency, reproducibility, or repeat-

ability and which is calculated as shown in Table I-67.

In practice, assessment of the consistency of questions is not as straightforward as it appears. Since the response in the same individual on two occasions is required, this repetition has its problems. If the period between the two interviews is too short, factors such as memory may influence the assessment. For example, the respondent may remember his replies, and although after recollection he may come to believe some of his earlier replies were incorrect, he may reply the same way the next time in order to be consistent. On the other hand, recollection between interviews for some individuals may lead them to change their mind. If the period between surveys is too long, real changes in their health will result in alteration in their replies. Seasonal factors can also play a part in this.

For questions on respiratory symptoms, reliability has been assessed in a number of studies. Most investigations report consistencies varying between 70% and 90%. Samet has extracted some reliability figures on phlegm production from several studies and these are shown in Table I-68. For his own study (last in the Table), he believes the poor reproducibility arose from excess reporting in the second interview.

Compared to questions on phlegm production, those on smoking are very reliable. Table I-69 shows some statistics on the reliability from four studies and as exemplified by Samet. The consistency statistics range from 95% to 99%.

Table I-67
CALCULATION OF CONSISTENCY

	Second Response	
	Positive	Negative
First response	a	b
Second response	c	d

$$\text{Consistency} = \frac{a + b}{a + b + c + d} \times 100$$

Source: Historical Definition

BIAS

There are two kinds of variation: that which occurs randomly and thus should act both positively and negatively with equal probability, and that which acts consistently in the same direction. The latter is called bias and is a frequent

source of problems in epidemiological studies. Bias can arise from differences between interviewers, from method of administration, from changes in the format of the questionnaire, and possibly, from seasonal effects.

INTERVIEWER DIFFERENCES

Since most studies endeavor to maintain consistency in their methodology, (i.e., not mixing postal with administered questionnaires, and not making drastic changes to the format during a study), the most common source of error is that associated with interviewer differences. Two methods of assessing observer differences have been used in the past. The first, which involves repeat interviews on the same person, is not practical for epidemiological surveys and suffers from the same memory and temporal change problems as does the assessment of consistency. The more widely used technique requires random allocation of respondent groups to different observers. Where necessary in analysis, account must be taken of age, smoking, and other relevant factors.

Observer differences have been reported by a number of workers. Most of those studies were undertaken before the introduction of the BMRC. One of the early ones, if not the earliest, was by Cochrane and colleagues who found a twofold difference in prevalence between four interviewers (23%-46%) for cough, and a threefold difference for sputum production (13%-42%) (5). In later studies, such as that by Lebowitz and Burrows among others, no or few differences were reported (14). However, in an investigation which looked at differences between two observers over the long term, Attfield and Melville found consistent evidence of bias amounting, for one question, to as much 10% on average over eight comparability trials (2). This occurred despite continued monitoring and correction.

The source of interviewer variation does not rest completely with the interviewer. Fairbairn and colleagues examined in detail the reasons for observer disagreement (7). They estimated 62% of the variation arose with the interviewer, 21% with the respondent, and the remainder was the fault of the question format. They reported that most of the observer errors arose from failure to keep to the briefing. Reasons given were:

- 1) wrong treatment of vague answers;
- 2) unwarranted probing or insufficient probing;

Table I-68
RELIABILITY OF RESPONSE TO PHLEGM QUESTIONS

Author/Date (Ref.)	Population	Questionnaire: Question	Reliability (%)
Fletcher, 1959 (10) Fairbairn, 1959 (7)	Postal employees, England	MRC: grade of phlegm	77
Morgan, 1964 (18)	Coal miners, England	PFR: AM phlegm PFR: persistent phlegm	77* 89
Holland, 1966 (13)	Coal miners, Wales	PFR: AM phlegm PFR: persistent phlegm MRC: phlegm, 3 months	80 81 82
Van der Lende, 1972 (24)	Population sample, Netherlands	MRC: phlegm, 3 months	91 +
Samet, 1978 (22)	Shipyard workers, USA	MRC: phlegm, 3 months Clinician: phlegm, 3 months	63 62

*Calculated from Table 2 (Samet article (21)).

+ Consistent response on four occasions during two years.
Source: Adapted from (21)

- 3) rewording of questions;
- 4) phrasing probing questions so as to bias reply;
- 5) forcing answers.

Attfield and Melville also analyzed the reasons for interviewer differences and came to the same conclusions as Fairbairn and co-workers (2). They blamed lack of clear instruction on the questionnaire for some of the errors and noted it had resulted in incorrect skipping of questions early on in their study. Since probing had resulted in errors, it was disallowed later in the study.

COMPARISON BETWEEN QUESTIONNAIRES

Literal comparison between results from different studies is unwise, but when very different questionnaires have been used, validity of the comparison is even more tenuous. In general, it can be said that questionnaires that differ greatly in wording or structure will lead to differing estimates of prevalence. Despite this, their individual validity, as measured by comparison with independent criteria, may be equally good. The evidence suggests that where wording and other changes are minor, differences in response are not great. For instance, Lebowitz and Burrows com-

pared the BMRC format with that of the NHLI and found nearly identical prevalences for similarly worded questions (14). In contrast, inconsistent prevalences were obtained on chest illness, for which the questions were worded differently.

SEASONAL EFFECTS

The most recent evidence on seasonal effects suggests they are not as great as once thought. Seasonal effects were reported several times twenty to thirty years ago in Britain. It is now believed that air pollution, rather than cold weather, was responsible for these effects since household coal-fired heating was then used extensively.

INTERVIEWER TRAINING

Interviewer training must not be skimmed in the undertaking of a study. The BMRC questionnaire instructions suggest that before embarking on a study, all interviewers should first study the questionnaire and instructions and discuss any points of difficulty (16). They should then listen to recordings that have been made "... of interviews based on the questionnaire." They go on to say that "interviewers should then apply the questionnaire to 10 or more subjects (such as hospital patients) who have at least some chest symptoms (since no difficulty arises with subjects

Table I-69
RELIABILITY OF SMOKING HISTORY

Author/Date (Ref.)	Population	Questionnaire: Question	Reliability (%)
Fletcher, 1959 (10) Fairbairn (7)	Postal employees, England	MRC: smoking status	98
Morgan, 1964 (18)	Coal miners, England	PFR: smoking status	95
Holland, 1966 (13)	Coal miners, Wales	PFR: smoking status MRC: smoking status	99 99
Samet, 1978 (22)	Shipyard workers, USA	MRC: calculated lifetime cigarette consumption	0.81*

*Correlation coefficient.
Source: Adapted from (21)

who answer all questions with a confident "no"). These interviews should either be witnessed by an experienced colleague or tape-recorded so that any mistakes or doubtful points can be corrected or clarified at leisure afterwards." We suggest experienced interviewers act as fake respondents so that new interviewers can practice. The former will know the problems and pitfalls and can introduce them in his replies so that the new interviewer's proficiency can be evaluated.

After the new interviewer has had his first experience in the field, his performance should be compared with experienced observers where possible.

Training must not cease with the introduction of the recruit into regular interviewing. What Bennett and Ritchie term "interviewer drift" can act to cause differences between observers (3). Interviewer drift occurs as the interviewer ceases to maintain his initial standards. As those authors note, "the more times an interviewer uses a given questionnaire, the more remote the training period becomes and the more he will forget his briefing." To avoid interviewer drift, the performance of the interviewers must be monitored periodically. Comparability trials, tape recordings, and special test sessions are all methods of assessing whether incorrect methodology has crept in. Van der Lende and Orie suggest that pairs of interviewers be formed to interview each other (25). They note "it soon becomes a sport to 'trap' each other. The interviewee tries to give answers that are difficult for the interviewer to handle. . . Of course, the teachers listen carefully,

and after such sessions we discuss the difficulties and errors made."

SELF-ADMINISTERED AND POSTAL QUESTIONNAIRES

Since one of the major biases in the application of questionnaires is that arising from observer differences, it would seem that elimination of interviewers through the use of a self-administered questionnaire would improve the reliability of the information obtained. Unfortunately, the elimination of one type of error through use of the self-administered questionnaire seems to be accompanied by the introduction of another kind of error. This problem, non-response, which is particularly prevalent in postal surveys, results in incomplete answers being obtained or the absence of any information on a large part of the study sample. For example, Fletcher and Tinker found in a mailed questionnaire survey that 25% of the subjects did not complete the entire questionnaire (11). When compared with an interviewer administered group, answers on cough, phlegm, dyspnea, and smoking habits were similar. A number of workers have achieved an excellent response through carefully planned and executed studies and so have shown the problem of nonresponse can be eliminated.

One great advantage of a postal questionnaire survey is economy. Samet has noted, ". . . large mailed surveys have been successfully performed which would have been otherwise infeasible. . ." (21) Against this we have the possible disadvantages that completion is not under the

researcher's control; that the wrong person (such as a spouse) might complete the questionnaire for the designated respondent; or that a respondent's reply might be influenced by family members. One further disadvantage is that self-completion forms must be simpler than interviewer-administered forms as there is no knowledgeable person to guide the respondent. On the other hand, greater sensitivity is claimed for the self-completion form by a number of researchers. Mittman and co-workers report on such a case (17). Mork reviews the validity and reproducibility of the self-administered questionnaire and discusses other problems (19).

CONCLUSION

As Feinstein has stated, "History taking, the most clinically sophisticated procedure of medicine, is an extraordinary investigative technique: in few other forms of biological research does the observed material talk. . . . The acquisition of data by this verbal method is far more complex than by the techniques of physical examination or laboratory tests." The techniques and procedures outlined in this section aid in making the data acquired through questionnaires as reliable and valid as possible.

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LABORATORY ASSESSMENT OF RESPIRATORY IMPAIRMENT FOR DISABILITY EVALUATION

Brian Boehlecke

INTRODUCTION

This chapter will consider the usefulness and limitations of various laboratory examinations in the assessment of impairment due to respiratory disease. Overall disability determinations must be based on socioeconomic and psychologic factors as well as medical examination and objective laboratory test results.

To appropriately screen large numbers of subjects, a laboratory test should meet certain requirements (79). The cost should be reasonable—relative to other tests giving the same or comparable information. The test must be safe, relatively simple, and acceptable to the subject population. Finally, the yield of useful information should be high. Several aspects must be considered to determine how well a test meets this last requirement: (a) The test should be objective, i.e., results should be independent of subject motivation and cooperation. Bias of the technician administering the test or the observer interpreting the results should also have little influence. Clearly no laboratory test of pulmonary function is completely objective under these criteria (15). If a subject is apprehensive while performing the test, physiologic responses may be altered. Thus, hyperventilation during an exercise test may be caused by anxiety or deliberate noncooperation as well as cardiopulmonary impairment. (b) The test should be reproducible. Variation in results, when multiple measurements are made on an individual, stems from both the true biologic variability of the function measured and measurement error induced by the equipment or the observer (15). Equipment and techniques must be calibrated and standardized so that results obtained in different individuals and in different laboratories can be directly compared. (c) The test must measure the biologic function of interest. Many medical tests provide only an indirect measure of the biologic func-

tion of interest. For example, the relationship between "disability" and measures of physiologic impairment is far from direct.

Impairment is generally accepted to mean reduction in function below that found in health. For objective tests to accurately quantitate impairment, the level of function prior to the onset of injury or illness must be known or an accurate prediction for "normal" function in health must be available. Often, neither condition is fulfilled. Disability may be considered to be present when an individual lacks the ability to perform a certain level of a specific task. Reduced efficiency for accomplishing a task may also constitute disability if the worker experiences undue distress or risk to well-being while performing the task. However, the severity of symptoms constituting undue distress is as much a social as a medical decision. The importance of distinguishing impairment from disability has been discussed by several authors (8)(14)(26)(33).

Laboratory tests of function may be used to assist disability evaluation in two ways. The measured level of function remaining may be compared to the demands of a given activity. Test results may also be correlated with independent measures of disability such as symptoms experienced while performing a given task. However, test results and symptoms may not be closely related for several reasons (14). In healthy individuals, pulmonary function capacity greatly exceeds daily activity performance requirements. A significant loss in function can occur before symptoms are experienced during usual levels of exertion (Figure I-22). Also, if more than one organ system is impaired, a test measuring the function of only one system will not correlate closely with the overall function of the individual. Individual variability in psychological response to illness and sensations of discomfort also contribute to the lack of direct correspon-

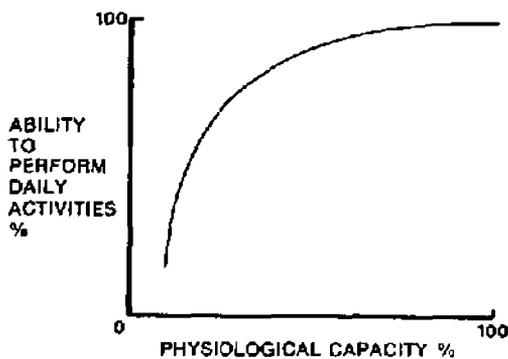


Figure 1-22. Idealized relationship between physiologic capacity and ability to perform daily activities.

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dence of symptoms and objective tests of function. This is especially true when economic benefits are involved. Also, in conditions characterized by exacerbations and remissions (e.g., asthma), incapacity for work may be determined more by the frequency and severity of attacks than the level of function measured on a given day.

With these principles in mind, individual tests of pulmonary function and their use in disability assessment will be discussed.

SPIROMETRY

One of the most widely used objective tests of pulmonary function is the ability to move air as measured by spirometry. The technique requires the subject to make a full inspiration, to blow out as hard and rapidly as possible into the spirometer, and to continue exhaling until he has breathed out as much gas as possible. Measurements which can be made from this maneuver include the total volume of gas exhaled or the forced vital capacity (FVC), the volume of gas exhaled during the first second (FEV_1), and flow rates, i.e., the rate at which gas is being expelled at various points during the forced vital capacity maneuver. Results of this test clearly depend on a subject's ability to understand the maneuver, to completely fill his lungs prior to beginning the exhalation, to sustain a maximal effort during the exhalation, and to continue the effort until he has completely emptied his lungs. Results also depend on the number of maneuvers the subject performs, adequacy of coaching, and equipment characteristics—including resistance to air

flow and inertia. The technique used for measuring the volumes and flows, including start-of-test and end-of-test criteria also influences results. Detailed reports of expert opinion on proper techniques and instrumentation standards have been presented (6)(27), and recommendations of standardized methodology have been prepared for the National Heart, Lung and Blood Institute (23). Spirometers accurate to within 3% of reading are currently available.

If an individual performs three maneuvers with values for FEV_1 within 5% of each other, further maneuvers add little information and do not significantly reduce the variability of results for the session. If a subject repeats spirometry several times over a single day or over several weeks, the coefficient of variation for this FVC and FEV_1 , averages 2.5% to 3.0% (13)(46). Variability for flow rate at the mid-point of vital capacity is significantly greater, ranging from 6% to 8% when studied over a single day, to approximately 12% when studied over several weeks. Flow rates at lower lung volumes are even more variable. Thus, in terms of reproducibility, the standard forced vital capacity and FEV_1 measurements are most advantageous.

The ratio of FEV_1/FVC is a useful measure of the presence of obstruction. Many pathologic processes reduce the ability of the respiratory system to generate normal flow rates, especially on expiration. Although the FEV_1 may be reduced in absolute terms, because of the wide range of normal values and the usual lack of baseline data, small decrements in FEV_1 may not be easily detected. This is especially true if the subject's pulmonary function was significantly above the mean predicted for persons of the same sex, age, and physical characteristics, prior to the onset of his decrement. In obstructive lung disease, the FVC is often not reduced to the same extent as the FEV_1 ; therefore, the ratio of FEV_1 to FVC provides a more sensitive index of obstruction. Prediction equations for FEV_1/FVC ratio have been published. However, the variability of the FEV_1/FVC ratio has not been examined as thoroughly as each separate parameter. It is not appropriate to consider the ratio of FEV_1 to FVC alone, since restrictive impairment (which limits the total volume of air that can be expelled from the lungs, but not the rate at which it is expelled) would not be detected.

Spirometric values have an inherent vari-

ability in the same individual, even in the absence of changes in factors known to influence pulmonary function. Airway spasm induced by infection, allergic reaction, or inhalation of toxic substances can produce marked transient variations in ventilatory function measured by spirometry. Therefore, for impairment assessments, spirometry should always be done when a patient is as near to a "baseline" state as possible; i.e., free from infection or medication known to affect pulmonary function. If medication might reverse impairment, spirometry should be repeated after the administration of a bronchodilating drug. Based on the variability in normal subjects, an increase of at least 10% in FEV₁ is necessary to be considered a significant response to medication. Complete discussions of the clinical implications of spirometric findings can be found in standard textbooks of pulmonary diseases (7)(17).

Large groups of persons, in whom there is no reason to suspect pulmonary impairment, have been studied to establish the normal range for spirometric values. Studies of this kind have established that factors of age, height, sex, and race, all influence spirometric values in healthy individuals. Several recent studies using modern spirometric equipment and techniques have been published (39)(52)(53)(60). Prediction equations for spirometric values obtained in the most recent of these studies are shown in Figure I-23. For any given age and height, there is a range of

For males ≥ 25 years of age:

$$\text{FVC (liters)} = 0.065 \text{ Height (cm)} - 0.029 \text{ Age (years)} - 5.459, \text{ S.E.E.} = 0.601$$

$$\text{FEV}_1 \text{ (liters)} = 0.052 \text{ Height (cm)} - 0.027 \text{ Age (years)} - 4.203, \text{ S.E.E.} = 0.541$$

For females ≥ 20 years of age:

$$\text{FVC (liters)} = 0.037 \text{ Height (cm)} - 0.022 \text{ Age (years)} - 1.774, \text{ S.E.E.} = 0.519$$

$$\text{FEV}_1 \text{ (liters)} = 0.027 \text{ Height (cm)} - 0.021 \text{ Age (years)} - 0.794, \text{ S.E.E.} = 0.434$$

S.E.E. = Standard Error of the Estimate

Figure I-23. Prediction equations for spirometry in healthy subjects.

Adapted from Knudson, R. J., Slatin, R. C., Lebowitz, M. D., Burrows, B. The maximal expiratory flow-volume curve: Normal standards, variability, and effects of age. *Am Rev Respir Dis.* 1976, 113:587-600.

values for FVC or FEV₁, even among healthy individuals. The lower limit of normal for a given age and height is often defined as that value above which 95% of healthy individuals in a population would fall. This is approximately

the mean value minus 1.64 standard errors of the estimate. From the magnitude of the standard error of FEV₁, it can be shown that any value above approximately 80% of the mean predicted value is considered "normal" by this definition. This points out the wide variability in normal function and the inherent difficulty in assessing impairment of an individual subject when his previous pulmonary function values are not known.

Even recent studies of healthy subjects have had limitations. Studied groups have generally been composed primarily or solely of Caucasians living in a specific region, and no effort has been made to assess possible influences of social class or occupation on respiratory function. Petersen et al. studied asymptomatic, nonsmoking, working coal miners (60); no significant differences were found between this group and others which were more heterogenous for occupation. Several studies have demonstrated the forced vital capacity and FEV₁ of black males are somewhat lower than those for white males of the same age and standing height (1)(19)(42)(58)(64). The FEV₁ of black males has been found to be approximately 85% to 90% of that for their white counterparts. Although less information is available, a similar relationship may apply in females. However, further study is necessary because application of a general scaling factor would not be totally accurate; only a separate prediction equation, based on a large study of healthy blacks, will produce accurate predictions (66). The ratio of FEV₁ to FVC does not seem to be affected by race. The FEV₁ and FVC are decreased proportionately so the ratio remains relatively unchanged.

Another spirometric measure which has been used extensively is maximum voluntary ventilation (MVV), or the maximum amount of air which can be breathed out in one minute. The test is usually performed for 12 seconds and the results extrapolated to one minute. The MVV is more difficult for the subject to perform than a single forced vital capacity maneuver, and, for that reason, results are more variable. In some subjects the maneuver produces dizziness, wheezing, or chest pain. Even with good cooperation, results are influenced not only by the state of lungs, but also by chest wall musculature, neurologic function, coordination, the presence of cardiac disease, and other factors. Although the learning effect for the MVV ma-

neuver is greater than that for the forced vital capacity, the second MVV was, on average, 98% of the best effort out of 3 in 425 persons (25). In healthy subjects there is a close relationship between the FEV₁ and the MVV, and a reasonable approximation of MVV can be obtained by multiplying the FEV₁ by 40. However, when an abnormality outside the lung limits the MVV, it may be significantly lower than 40 times the FEV₁. This comparison serves as a useful check on the validity of the MVV and aids in identifying an inability to understand directions; outright malingering; or the presence of other conditions such as heart disease or muscular weakness, which may affect the MVV more than the FEV₁. Because the MVV maneuver requires sustained effort, it might be expected to correlate better with overall capacity for work than a single expiratory maneuver. However, because of the arduousness of the maneuver, the greater variability, and the increasing availability and use of exercise tests which produce more information, the MVV has fallen out of favor. Many well-equipped pulmonary function laboratories no longer routinely perform this test. Although prediction equations for MVV in normal subjects exist (males (40); females(43)), none of the more recent surveys of pulmonary function in normals utilized the MVV maneuver. Standardized apparatus and methodology have been suggested for those who continue to use the test (23).

DIFFUSING CAPACITY OF THE LUNG (D_{LCO})

The diffusing capacity of the lung is operationally defined as the amount of gas transferred from the alveoli to the pulmonary capillary blood per unit of time per unit gradient of pressure difference. Although in practice we are most interested in the diffusing capacity of the lung for oxygen, it is difficult to measure this directly, and a good approximation can be obtained by using carbon monoxide. The test is useful because in many infiltrative diseases, predominantly affecting the parenchyma of the lungs rather than the airways, spirometric values may be relatively well preserved, even though the lung's efficiency for transferring gas is severely impaired. Although there are several variants of the procedure—including those where subjects breathe normally at rest or during exercise—the technique commonly used today involves a single breath: the subject exhales to empty his lungs completely; breathes in a mixture containing a

low concentration of carbon monoxide and a relatively inert gas such as helium; holds his breath for approximately 10 seconds; and then begins to exhale rapidly. After gas which resided in the upper airways (the non-gas exchanging portions of the respiratory system) has been exhaled, a sample of end expiratory, or so-called "alveolar" gas, is collected and analyzed for carbon monoxide and helium concentrations. The amount of carbon monoxide absorbed during the breath holding period can be calculated, and the alveolar concentration of CO estimated from the measured concentration of helium in the expirate. From these values, the diffusing capacity for carbon monoxide is calculated. Standardized methodology has been suggested for this test (23).

Many technical and biologic factors, other than the condition of the lung's "diffusing surface," affect the results. Technical factors include the duration of breath-holding, the method used to measure this period, and the timing and volume of the alveolar gas sample collected. Also important is the calibration of the analytical instruments measuring gas concentrations. Biologic factors include the lung volume and alveolar pressure during breath-holding and the "back-pressure" of venous blood carbon monoxide content. The latter may be elevated in cigarette smokers. The volume of pulmonary capillary blood, the blood hemoglobin concentration, and to some extent the cardiac output, also affect results. Uneven distribution of ventilation, while having a more significant affect on steady state methods, does affect the diffusing capacity measured by the single breath technique.

Measurement of D_{LCO} is generally less reproducible than spirometry. The coefficient of variation for repeat tests on an individual in the same laboratory have been approximately 5%-6% over a single day and 10% over several months (9)(34)(57). When identical gas samples were sent to 11 different laboratories for analysis and calculation of a simulated D_{LCO}, results varied from 46% to 171% of the "true" D_{LCO} (16). Although predictions for normal values of D_{LCO} are available (17), they are less well documented than those for spirometry. The variation of values among healthy individuals is large, and the "normal range" includes values down to approximately 70% of mean predicted. Additionally, technical and biologic factors explained above may produce alterations in the value of the D_{LCO} independent from lung function alterations. However, because the test is non-invasive

and produces information supplemental to spirometry, it is still useful in certain conditions despite its imprecision.

ARTERIAL BLOOD GASES

Measurement of arterial blood gas tensions gives an indirect estimate of the adequacy of gas exchange. Sampling of arterial blood from a peripheral artery, such as the radial or brachial, is relatively simple and causes only minor discomfort. Risk of damage to the vessel and thrombosis; formation of a large hematoma at the site of puncture; inadvertent damage to an adjacent structure such as a nerve; or infection at the site where the indwelling catheter is placed, are minimal. A good description of techniques and calibration procedure is provided in Kanner and Morris (38). Basically, the technique consists of obtaining arterial blood under sterile and anaerobic conditions, and either analyzing it immediately for oxygen, carbon dioxide, and pH on standard electrodes, or storing it under iced conditions and performing the analysis within approximately one hour. It has been reported that the oxygen tension in properly iced arterial blood falls only 4 torr (mm of mercury) in 12 hours when the initial value is in the range of 85 to 100 torr (84). Samples should always be analyzed in duplicate and should agree for pH to within $\pm .01$ pH unit and for PO_2 and PCO_2 to within ± 2 torr. The electrodes must be calibrated daily with precision gases; for some equipment, the membrane factor (which corrects for differences between measurements of gases and blood) must be determined by using tonometered blood. Although possibilities for technical error in the analysis of arterial blood gases are numerous, many of the problems arise at the time the blood is sampled or in its handling prior to laboratory analysis. Blood may be sampled from a vein rather than an artery, resulting in spuriously low results for oxygen tension. If blood is exposed to room air after sampling, the measured oxygen tension will be falsely elevated.

Assuming blood has been properly collected and analyzed, inherent biologic variability still occurs, both among healthy individuals and within a given individual sampled at different times and under different conditions. Changes in the pattern of a subject's respiration can alter the alveolar and thereby the arterial oxygen ten-

sion without any change in the intrinsic function of the lung. Altered patterns of respiration can also affect the distribution of ventilation-perfusion ratios and thereby alter arterial blood oxygen tension. A patient's posture at the time blood is sampled also affects results. Arterial oxygen tension is usually slightly lower with the subject supine, probably due to alterations in ventilation-perfusion ratios throughout the lungs. This effect can be marked in obese persons who do not have any apparent intrinsic lung pathology. Falls of arterial oxygen tension of up to 39 torr were seen in severely obese subjects when they assumed a recumbent position (65).

Table I-70

EFFECT OF ALTITUDE ON BAROMETRIC PRESSURE AND AMBIENT PARTIAL PRESSURE OF OXYGEN

Altitude Above Sea Level (feet)	Barometric Pressure (mm Hg)	Ambient PO_2 (mm Hg)
0	760.0	159.0
1,000	732.9	153.5
2,000	706.7	148.0
3,000	681.1	142.7
4,000	656.4	137.5
5,000	632.4	132.5
6,000	609.1	127.6
8,000	564.6	118.3
10,000	522.7	109.5
12,000	483.5	101.3

Adapted from Kanner, R. E., Morris, A. H. Clinical pulmonary function testing, Intermountain Thoracic Society, 1975.

The effect of altered inspired oxygen tension is complex, but must be considered because subjects studied at different altitudes inspire different partial pressures of oxygen. As barometric pressure falls with increasing altitude, the partial pressure of inspired oxygen also falls (Table I-70). The decrease in ambient oxygen pressure does not produce an identical change in arterial blood oxygen tension or tissue oxygen supply. Persons exposed to increased altitude exhibit several adaptive mechanisms to attempt to maintain adequate delivery of oxygen to the tissues. These include an increased cardiac output and, after a period of time, an increased concentration of red cells in the blood. These and other changes increase the delivery of oxygen to the

tissues for any given level of arterial blood oxygen tension. Ventilation is also increased, but nevertheless, arterial blood oxygen tension is lower at altitude than it is at sea level. Table I-71 provides estimates of normal blood gases at various altitudes.

Age must be considered when interpreting arterial blood gases. Arterial blood oxygen tension decreases in healthy adults at an average rate of approximately 0.27-0.33 torr/year, so that mean predicted values at sea level decrease from approximately 95 torr for ages 20-29 to 80-85 torr at ages 60-69 (45)(48). Lower limits of normal, defined by the mean minus 2 SD are approximately 85 torr at age 20 and 75 torr at age 60. Each laboratory generally establishes its own range of normal for healthy individuals.

Subtle impairments in gas exchange may be detected by measurement of the alveolar to arterial oxygen gradient abbreviated as (A-a)PO₂. However, it too is altered by many of the factors already discussed and increases with age, rising from a mean at rest of approximately 5 torr at age 15 to approximately 20 torr at age 75. Variation among individuals is large; the normal range includes values at least 10 torr greater than the mean (48). This measurement is also sensitive to cardiac output and may change without any change in lung function. A change in cardiac output can result in an increase in the relative fraction of blood being shunted through anatomic or physiologic shunts and/or a decrease in mixed venous oxygen content. Both cause widening of the (A-a)PO₂.

To estimate biologic variability, blood gases were measured on two separate occasions in individuals resting on a bed, breathing room air (37). The coefficient of variation for each variable was then calculated from the standard deviation of the difference between the first and second measurements. For arterial blood oxygen tension, the coefficient of variation was 3.6% and for PaCO₂, 3.4%. The alveolar to arterial oxygen pressure gradient had an even larger variability, with a coefficient of variation of almost 19%. Thus, although (A-a)PO₂ may be sensitive to changes in gas exchange within the lung, it is also highly variable.

In summary, analysis of arterial blood gas tensions and pH is a valuable tool for studying pulmonary system function. However, at the present time, methods for calibration and techniques are not fully standardized and numerous

factors must be considered when interpreting results. When tests from different laboratories are to be compared, it is imperative that techniques be as nearly identical as possible. It is recommended that blood be drawn from patients in a sitting position, due to the large falls in arterial oxygen tension which may occur in the recumbent position, especially in overweight subjects. Although the alveolar to arterial oxygen gradient may be a sensitive indicator of gas exchange abnormalities within the lung, it is highly variable in normal individuals and is no more predictive of limitation than other parameters more easily measured.

EXERCISE TESTING

Exercise testing is useful in clinical medicine in several ways. Certain patterns of response to exercise aid the clinician in differentiating pulmonary from cardiac impairments, or in assessing relative contributions to overall limitation when combined impairments are present. Symptoms or subtle abnormalities in function may not be detectable under resting conditions because the pulmonary and cardiovascular systems normally have an excess of functional capacity above demands. With the increased stress of exercise, use of abnormal compensatory mechanisms or inability to achieve a normal level of performance may be detected.

The ability to perform sustained work is dependent upon adequate gas exchange with the atmosphere. Although brief periods of work can be performed without the use of oxidative metabolism by the tissues, this process is highly inefficient, rapidly depletes substrates, and results in buildup of metabolic products such as lactate. Several linked processes are necessary to supply oxygen to the tissues and to rid the body of carbon dioxide. These include proper mechanical functioning of the chest and lungs, effective matching of deoxygenated venous blood with fresh gas in the alveoli, adequate diffusion of gases across the alveolar membrane, and an adequate total volume of blood being pumped per minute. Also required is the proper neurochemical monitoring and control of the respiratory system to maintain ventilation at a level appropriate for metabolic demand. Finally, oxygenated blood must be appropriately distributed to match tissue requirements. Normal exercise response requires adequacy and coordination of all these functions. Several excellent

Table I-71

NORMAL ARTERIAL BLOOD GAS VALUES

	Sea Level	Salt Lake City (altitude 1400 m)	Denver, Colorado (altitude 1580 m)
PaCO ₂ (torr)	80-100	68-85	65-75
PaCO ₂ (torr)	35-45	34-40	34-38
pH	7.35-7.45	7.35-7.45	7.35-7.45

Adapted from Kanner, R.E., Morris, A.H. Clinical pulmonary function testing, Intermountain Thoracic Society, 1975.

reviews of exercise physiology have been produced recently (36)(70)(76).

Adequate exercise testing requires that major muscle groups be utilized so that sufficient stress is placed on the cardiovascular and pulmonary systems to detect abnormalities not seen with lesser demands. The amount of exercise, i.e., the amount of work being done, must be quantitated in a manner which allows comparison of results between individuals and between different laboratories. This is best done by using the rate of oxygen consumption as the index of energy expenditure. The influence of body size on oxygen consumption can be partially controlled by expressing oxygen consumption per unit body weight or as a multiple of resting requirements. Most of the useful information gleaned from exercise testing can be obtained with a few simple measurements. During exercise, measurements should be obtained allowing calculation of heart rate, respiratory rate, total minute ventilation, oxygen uptake, and carbon dioxide production. Constant electrocardiographic monitoring and periodic blood pressure measurements should be performed during prolonged exercise. Monitoring arterial blood gases and pH during exercise allow more sophisticated interpretation of results, which may be helpful when impairment is minimal, or when the underlying diagnosis is not known.

NORMAL PHYSIOLOGIC RESPONSES TO EXERCISE

As energy expenditure increases, exercising muscles utilize more oxygen. An increase in oxygen available to muscle can be achieved by: 1) an increase in the oxygen content of arterial blood (CaO₂ entering the muscle; 2) a greater extraction of oxygen from each unit volume of blood passing through the muscle; or 3) an increase in total blood flow (Q) to the muscle. Because hemoglobin is almost completely satu-

rated with oxygen at the normal arterial blood oxygen tension (Figure I-24), little increase in CaO₂ can be attained. The extraction of oxygen does increase such that the saturation of hemoglobin in mixed venous blood may decrease from 75% at rest to 25-35% or lower at maximal exercise. This second mechanism for increasing oxygen delivery is limited by the inability of normal metabolic pathways to function below a critical level of tissue oxygen tension.

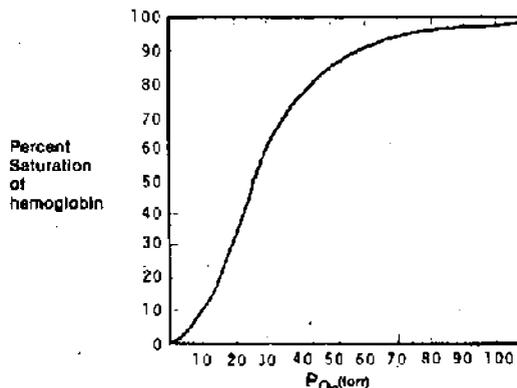


Figure I-24. Hemoglobin-oxygen dissociation curve at 37°C and pH = 7.40.

An increase in flow is accomplished by several mechanisms: a marked redistribution of blood flow occurs—the relative share to exercising muscles increases and that to certain organs e.g., gut and kidney, decreases. The total amount of blood pumped by the heart per minute (cardiac output) also increases. Both heart rate and amount of blood pumped with each heartbeat (stroke volume) increase. Stroke volume rises to near maximum at relatively low levels of exercise, so further gains in cardiac output are the result of increasing heart rate. Overall heart rate increases approximately linearly with oxygen consumption.

To supply the increased amount of oxygen necessary to re-oxygenate venous blood, ventilation must also rise. Minute ventilation rises

linearly with oxygen consumption as exercise level is increased (Figure 1-25), and no fall in arterial blood oxygen tension occurs during steady state exercise.

The response of heart rate and ventilation to exercise varies among healthy individuals; tables summarizing the "normal range" from several studies appear in Cotes (17) and Jones *et al.* (36). Differences between individuals depend on many factors including body size, total body hemoglobin content, and habitual level of physical activity. These factors account for most of the differences found between sexes and races. When comparisons are made, work rate must be quantitated by oxygen consumption, not by apparent external work achieved. Obese subjects expend more energy than lean persons for a given level of external activity (30). Even if weight is considered, the extra work done in accelerating the limbs is difficult to quantitate.

The response to exercise of a given individual also varies. Jones and co-authors reported that the oxygen consumption may vary by $\pm 4\%$, the heart rate by $\pm 3\%$ and minute ventilation by $\pm 4\%$ when measured on successive days at the same level of exercise (36). Anxiety tends to raise heart rate and minute ventilation for a given level of exertion, as does a recent large meal. The heart rate response to exercise has a normal diurnal variation with lowest values occurring in the early morning. Many medications alter cardiovascular response to stress.

Additionally, the type of exercise performed may affect the relationship between heart rate and oxygen consumption. The energy expended walking on a level treadmill and walking on the floor at speeds of 1.75 to 3.5 miles per hour is the same (63). However, Jessup found heart rates to be higher when pedaling at 80 rather than 50 revolutions per minute on a bicycle ergometer at low levels of oxygen consumption (35). Although others disagree, Michael and co-workers found a higher heart rate at a given level of oxygen consumption when measured on a treadmill (49). To be strictly comparable, studies should utilize the same method of exercise.

MAXIMAL EXERCISE CAPACITY IN HEALTH

In healthy subjects, the maximal level of exertion is heralded by the onset of an intolerable sensation of shortness of breath. However, ven-

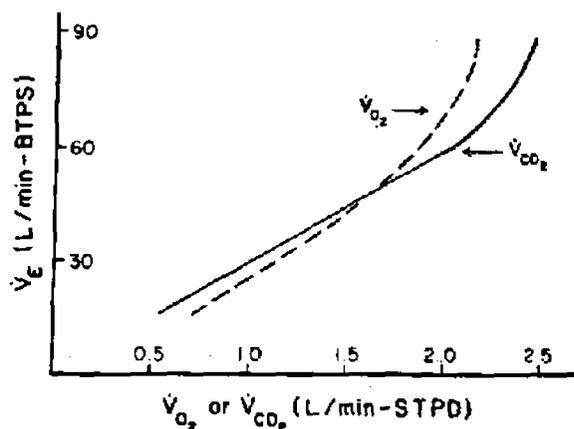


Figure 1-25. Relationship between ventilation (V_E) and oxygen consumption (V_{O_2}) or carbon dioxide production (V_{CO_2}) during exercise.

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tilation at maximal exertion seldom exceeds 60-80% of the resting maximal voluntary ventilation (17) and arterial blood oxygen tension does not fall from resting levels (76). Thus, neither mechanical limits to ventilation nor gas exchange capacity within the lungs determine the end point for exercise. The end point is reached when the cardiovascular system can no longer supply oxygen at a rate sufficient to meet aerobic energy requirements.

As oxygen demand increases, the mechanisms previously discussed increase the supply. At high levels of demand only an increase in cardiac output is effective in significantly increasing supply. When the heart rate reaches its maximum value, cardiac output no longer increases and oxygen supply to exercising muscles has reached its limit. Further increases in energy expenditure must be met with anaerobic metabolism. Lactic acid is produced and excess hydrogen ions are buffered by bicarbonate producing carbon dioxide. To maintain a normal blood pH, ventilation must increase to eliminate this excess CO_2 . The increase in ventilation is perceived as "inappropriate" and the subject terminates the exercise. Thus, although the sensation of shortness of breath appears to limit exercise capacity, the underlying cause is cardiovascular not pulmonary.

Exactly why a certain level of ventilation is perceived as "inappropriate" is not known. The dyspnea index (D.I.) has been defined as the

minute ventilation divided by the resting maximal voluntary ventilation. Several authors have found a close correlation between the dyspnea index and shortness of breath during exercise (29)(44). If the dyspnea index is less than 35%, very few subjects complain of shortness of breath; however, if the D.I. is greater than 50%, virtually all do. Thus, the perceived "stress" of exercise seems related to how much of a subject's ventilatory capacity must be used to perform the exercise. Campbell and Howell have shown that dyspnea (the sensation of shortness of breath) is related to an imbalance between the amount of force exerted on the lung and the resulting displacement (10). A "length-tension inappropriateness" can result from stiffening of the lung or increase in resistance to airflow in the tracheo-bronchial tree. The increased respiratory rate during maximal exertion may somehow contribute to the perception of dyspnea by this mechanism. Clearly individuals differ in the perception of unpleasant sensations. Limitation of exercise by the subjective sensation of dyspnea is thus influenced by the subject's previous experience, his understanding of "normal" function, his mental attitude, and his familiarity with the type of exercise performed.

Maximum oxygen consumption reaches a peak in the late teens, remains relatively stable until the mid-twenties and then begins to decrease. Although other factors may play a role, a decrease in the maximum achievable heart rate is the major reason for this decline. Oga and co-workers found a decrease of 0.4 ml/kg/minute per year in maximum oxygen consumption in healthy men (56). All these factors, including some which are difficult to quantitate (e.g., habitual level of physical activity), result in a range of exercise capacities in healthy subjects. Maximal oxygen consumption can be measured directly or estimated by projecting the relationship between heart rate and oxygen consumption (\dot{V}_{O_2}) measured during submaximal exercise to a predicted maximum heart rate. Maximum heart rate can be predicted from age alone by a relationship derived from studies of normal subjects (4).

EXERCISE CAPACITY IN THE PRESENCE OF CARDIAC OR PULMONARY IMPAIRMENT

Subjects with significant heart disease often have diminished exercise tolerance. This may be

due to an inability to raise cardiac output in the presence of a diminished stroke volume. Heart rate rises abnormally rapidly, relative to exertion levels, and reaches its predicted maximum at a lower than normal work load (76). However, subjects with pulmonary impairment often do not achieve heart rates approaching their predicted maximum when they feel constrained to terminate exercise. Instead they reach ventilatory limits due to a diminished capacity for ventilation; an increased demand for ventilation not directly related to circulatory factors; or both.

In patients with obstructive lung disease, a significant decrease in ventilatory capacity results in an inappropriately high dyspnea index for a given level of exertion. Thus, maximal exercise capacity may be diminished. An impairment in gas transfer capacity may further lower exercise capacity by requiring increased ventilation to maintain adequate gas exchange. However, the contribution of this latter impairment is difficult to predict from resting measurements because gas exchange often improves during exercise in patients with obstructive pulmonary impairment. This is probably due to improvement in the distribution of perfusion relative to ventilation in the lungs during exercise (69).

The capacity of the lung to exchange gas, as estimated by the diffusing capacity, does not contribute to exercise limitation in normal subjects (67). For subjects with severe diffusion impairment, limitation of exercise should theoretically appear rather abruptly at some critical level of oxygen consumption. This would be expected because oxygen saturation of end pulmonary capillary blood is well maintained until oxygen consumption reaches this critical level; then saturation drops rapidly. The critical level of \dot{V}_{O_2} is reduced as diffusing capacity decreases. In persons with primarily obstructive impairment, mechanical ventilatory limits are reached before the critical level of \dot{V}_{O_2} is attained. However, in subjects with severe diffusing capacity impairment, arterial blood oxygen tension often falls during exercise. This hypoxemia may cause an increased ventilatory response by acting on receptors in the carotid body, and the excessive ventilation results in dyspnea and limitation of exercise tolerance. The decrease in blood oxygen tension may not significantly affect tissue oxygenation because of the shape of the oxygen-hemoglobin dissociation curve (Figure I-24). A decrease in arterial blood oxygen tension from

95 torr to 55 torr decreases saturation only about 10%. If Pa_{O_2} falls below 55 torr, oxygen delivery may be only slightly diminished, but excessive ventilation relative to the level of exertion may diminish exercise tolerance.

ESTIMATION OF OVERALL FUNCTIONAL CAPACITY

A straightforward approach to estimating overall functional capacity is to measure maximum exercise tolerance directly. Theoretically, maximum exercise capacity could then be compared to the demands of any activity and the relative "stress" of that activity for the individual determined.

The direct measurement of maximum exercise tolerance has several disadvantages. The procedure is time consuming, extremely uncomfortable for the subject, and has some risk of precipitating a cardiac emergency. In a group of subjects over 60 years old, progressive exercise tests had to be terminated due to electrocardiographic signs of myocardial ischemia, or significant alterations in cardiac rhythm, in 70% of the males and 55% of the females (18). Therefore, most investigators have attempted to estimate maximum capacity for exercise from measurements made during submaximal exercise or at rest. Submaximal exercise tests have proven to be relatively safe, with only 16 deaths reported in 170,000 studies (70). However, even submaximal exercise testing requires the presence of a physician and is generally more expensive and less widely available than resting tests of pulmonary function. Therefore, considerable effort has been made to relate objective tests of function made at rest to symptoms experienced during exercise.

VALIDATION OF OBJECTIVE TESTS BY COMPARISON WITH SYMPTOMS AND EXERCISE TOLERANCE

Comparison of objective function tests with symptoms experienced during exertion is necessary to validate these tests as predictors of overall functional capacity. The correlation of symptoms with impairment—as measured by these tests—is often not close due to the complex interaction of compensatory mechanisms and the variation in individual perception and interpretation of "abnormal" sensations. This is especially true when more than one organ system is impaired.

Special problems may also be encountered when evaluating disability applicants. Cotes studied 125 miners applying for disability awards and 125 miners seen in a chest clinic for other reasons (15). Those who had applied for disability awards complained of more severe symptoms at a given functional level (as measured by FEV_1) than the control miners. Similar results were found in 50 consecutive cases evaluated for total disability due to pulmonary disease under the Social Security system (12). Clinical grade of dyspnea was based on whether shortness of breath occurred only when hurrying (grade 1), when walking at a normal pace on level ground (grade 2), or with ordinary activities including dressing (grade 3). Those classified grade 2 differed little in mean function from those classified grade 3; in fact, the grade 3 group had higher mean values for the MVV and the FEV_1/FVC ratio. A group of clinic patients with grade 1 dyspnea who were not applying for disability benefits had an average FEV_1 to FVC ratio of 37% while claimants reporting grade 1 dyspnea had an average ratio of 52%. Lindgren and co-authors studied 100 randomly selected claimants for total disability due to lung disease or shortness of breath syndromes and 100 patients matched for age, sex, and degree of pulmonary function impairment (44). A clinical history was taken and the subjects observed during a standard level walk. Claimants more often overestimated (26% vs. 9%) the severity of their dyspnea compared to that observed during the exercise test.

Patients may also be poor judges of their own ability to perform activities. Sixty-two patients, 44 of whom had obstructive lung disease, and 18 of whom had an infiltrative lung disease without obstruction, were asked to estimate the distance they could walk, at their own pace, before having to stop due to shortness of breath, and the distance they could walk in 12 minutes (47). They were then asked to walk at their own pace as far as possible in 12 minutes. Results showed no correlation between the distance walked and either of the estimates. Thus it is difficult to correlate symptoms with function, especially in disability claimants.

Numerous attempts have been made to predict disability due to respiratory impairment from resting spirometric measurements. Two hundred and sixteen patients with obstructive lung disease and no other disabling conditions,

were separated into six functional classes by taking a detailed history (81). Most closely correlated with the clinical degree of pulmonary disability were the FEV₁ and the MVV, with correlation coefficients of .93 and .96 respectively. The authors derived an equation to predict the clinical degree of pulmonary disability based upon the MVV, FEV₁, age, and vital capacity. The overall correlation coefficient of the prediction, from the equation to the actual clinical grade, was high (0.83); however, individual variability was also high. Individuals judged clinically as class 3 were placed in classes 2 through 5 by the prediction equation.

In subjects with obstructive lung disease, maximum voluntary ventilation measured at rest correlates closely with symptoms during exercise (29). This does not necessarily hold true for subjects with interstitial lung disease and definite abnormalities in gas exchange, but without significant obstruction. Although maximum voluntary ventilation may be within the predicted normal range, such subjects often hyperventilate during exercise due to impaired gas exchange and thus have a decreased exercise tolerance (24). In these subjects, significant errors in estimating impairment can be made if the diffusing capacity is not also considered (22).

In another study, 30 men with obstructive lung disease—all of whom had an FEV₁/FVC ratio less than .55—were exercised to tolerance on a treadmill (28). Most closely correlated with the ability to exercise was the FEV₁. However, exercise tolerance varied widely for a given level of FEV₁. The correlation was higher between exercise ability and absolute FEV₁, than for the FEV₁ expressed as a percent of predicted (28) as McGarvin and co-workers also found (47). This is not surprising since exercise capacity is determined by function remaining, not the amount which has been lost. The importance of basing assessment of disability on remaining function has been stressed by several authors (15) (26).

The dyspnea index (exercise ventilation/maximum voluntary ventilation) has been found to correlate highly with the clinical grade of breathlessness during exercise (29). The dyspnea index was also studied by Lindgren and co-workers in their examination of 100 disability claimants together with patient controls (44). Impairments were mostly the obstructive type. The dyspnea index for patients who had no

shortness of breath during the standard exercise averaged 23%, with very few values above 35%. Those who complained of severe shortness of breath during the exercise had an average dyspnea index of 78% and all were above 50%. For a given severity of dyspnea during the exercise, the dyspnea index was 10% lower in the claimants than in the patients. Claimants expressed greater symptoms than patients at objectively comparable levels of stress, and the relationship between MVV (or FEV₁) and exercise capacity was different for the two groups. Thus, the FEV₁ and the MVV appear to be closely correlated with symptoms during exercise and exercise capacity for groups of subjects with obstructive lung disease. However, the relationship is highly variable for individuals and may differ between disability applicants and others. The ability to predict symptoms and exercise capacity from arterial blood gas studies has also been examined.

Teculescu and co-workers found that the FEV₁ correlated closely with resting arterial blood oxygen tension in 156 patients with symptoms of shortness of breath (75). A prediction equation for the Pa_{O₂} was developed, based on FEV₁ alone. However, the standard error of the estimate around the regression line was approximately 20%. Thus, the range of prediction for an individual was so large as to be clinically useless. The correlation was not improved when the FEV₁ was expressed as a percent of predicted.

Most workers have not demonstrated a direct relationship between arterial blood gas values and resting spirometry (68). Neukirch et al. did show some correspondence between the FEV₁ as a percent of predicted and blood gas abnormalities at a low level of exercise, but they could not accurately predict individual results due to wide scatter in the data (54).

Early studies of exercise tolerance showed no relationship between hypoxemia at rest or during exercise and the ability to exercise or the clinical degree of disability (50)(73). Studied subjects primarily had obstructive lung disease. Coates found no difference in resting Pa_{O₂} or Pa_{CO₂} between three groups of disability applicants with dyspnea ranging from grade one to grade three in severity (12). A study of patients with severe obstructive lung disease (maximum voluntary ventilation less than or equal to 35% of predicted) showed no correlation between arterial blood oxygen tension at rest or at

maximal exercise with the maximum work load tolerated (74). Subjects terminated exercise on the bicycle ergometer due to dyspnea; no subject experienced chest pain suggestive of angina. The alveolar to arterial oxygen tension gradient, when measured at rest or at the point of maximum exercise, also showed no correlation with the maximum work load tolerated. A similar study of subjects with less severe obstructive lung disease showed no correlation between the value of arterial blood oxygen saturation or carbon dioxide tension during exercise with the level of exercise (28).

Spiro and co-workers conducted a more detailed study of 20 subjects with moderately severe obstructive lung disease (mean FEV₁ equal to 49% of predicted); 20 very severely obstructed patients (mean FEV₁ to 24% of predicted); and 20 normals (71). Subjects performed progressive exercise on a bicycle ergometer, until having to stop due to shortness of breath or reaching 85% of maximal predicted heart rate. The normals all reached the heart rate end point; maximal exercise ventilation was, on average, 46% of the MVV predicted from the measured FEV₁. At the break point of exercise, moderately obstructed patients were found to be using 99% of their predicted maximum ventilation; severely obstructed patients were breathing at a level of 146% of the predicted maximum. Heart rate, at maximum exercise tolerated, was far below levels of predicted maximum for both obstructed groups. Thus, the major limitation to exercise in the obstructed subjects was ventilatory. The Pa_{O₂} and Pa_{CO₂} did not significantly change from rest to exercise in the moderately obstructed group. The severely obstructed group did show a fall in Pa_{O₂} from 69.7 torr to 60.9 torr, but this fall would not cause a significant change in arterial blood oxygen content, and so is unlikely to have been the cause of exercise limitation. The rise in lactate 5 to 10 minutes after maximal exertion (which is indicative of anaerobic metabolism) was less in the patient group than in the normals. None of the patients manifested a rise in ventilation relative to oxygen consumption, which indicates the anaerobic threshold has been reached. The authors concluded it was unlikely that the fall in arterial blood oxygen tension or anaerobic metabolism significantly influenced the end point of exercise for these patients.

In general, arterial blood oxygen tension is

not increased by training even though tolerance for exercise is improved (11)(59). Under some circumstances, even normal subjects may show a fall in Pa_{O₂} with exercise (61)(82). Young and Woolcock had healthy, young, non-smoking subjects, with normal pulmonary function, walk up stairs at 9 meters per minute (84). The mean arterial blood oxygen tension fell from 92 torr at rest to a mean lowest value of 65 torr during the first minute of exercise. The maximum fall observed was 33 torr. Thus, significant decreases in Pa_{O₂} may occur transiently during exercise in completely healthy subjects. Therefore, it is important to allow subjects to reach a steady state prior to measuring arterial blood gases in disability evaluation exercise tests. If this is not possible because a subject is unable to maintain the [chosen] exercise level, the study should be repeated at a lower level of exercise.

Arterial blood gas tensions are not correlated with other tests of pulmonary function in a manner which allows prediction of results for individual subjects. Also, they are only indirectly related to exercise limitation in most subjects, even those with severe obstructive lung disease. They may be more valuable in subjects with diffusion impairment and are useful in allowing more sophisticated analysis of exercise results when diagnostic considerations require detection of minimal levels of impairment. As indicated by changes seen in normals working at altitudes, "abnormalities" in arterial blood gases cannot be automatically equated with disability (26).

When evaluating the relationship between diffusing capacity and symptoms or exercise tolerance, careful distinction must be made between subjects with interstitial lung disease and those primarily with obstructive impairments and associated defects in gas transfer. Coates found no significant difference in diffusing capacity among three groups of applicants for Social Security disability benefits who had symptoms of dyspnea ranging from grade 1 to grade 3 in severity (12). However, only 15% of these subjects had interstitial lung disease; the remainder primarily had obstructive impairment. Diffusing capacity also showed no correlation with exercise tolerance (28) or fall in Pa_{O₂} during progressive exercise to maximal tolerance (71) in subjects with obstructive lung disease. However, in patients with interstitial lung disease without obstruction, diffusing capacity was

closely correlated with the maximal distance walked in 12 minutes, and the patient's estimate of the stress of the exercise (47). Wilson was able to estimate incapacity in patients with primary gas exchange impairment—with moderate accuracy—from an equation based on D_{LCO} (80). Wehr & Johnson included D_{LCO} in a theoretical model predicting maximal oxygen uptake for persons with lung disease (78). Thus, diffusing capacity may be useful in estimating exercise capacity in subjects with interstitial lung disease. It is generally not helpful in those with primarily an obstructive impairment.

In summary, objective measures of pulmonary function and symptoms during exercise do not correspond closely in individual subjects. For groups of subjects, the FEV_1 and MVV correlate most closely with symptoms in those with obstructive lung disease; in those with interstitial (restrictive) lung disease, the diffusing capacity correlates best. Arterial blood gas studies are not helpful in predicting symptoms or exercise tolerance in patients with obstructive lung disease. They may be useful in patients with a predominant impairment in gas exchange.

PREDICTION OF MAXIMAL EXERCISE TOLERANCE

In persons with significant pulmonary impairment, exercise tolerance is most often determined by a ventilatory limit (71). When minute ventilation reaches a critical level relative to maximal ventilatory capacity, the subject experiences symptoms of dyspnea. Exercise tolerance may be reduced by a decrease in maximal ventilatory capacity; an increased demand for ventilation relative to energy expenditure; or a combination of both. An increased demand for ventilation may be caused by impaired gas exchange in the lungs. Wright developed an equation to predict maximal oxygen consumption from measures of ventilatory capacity (the MVV) and gas exchange (the ventilatory equivalent for oxygen or $\dot{V}E_{O_2}$) (83). The ventilatory equivalent is the minute ventilation divided by oxygen consumption and should be elevated if gas exchanged is impaired. Armstrong et al. applied this equation using MVV measured at rest and the ventilatory equivalent measured during submaximal exercise (2)(3). Maximal oxygen consumption estimated in this way correlated closely with that measured directly in 70 subjects with lung disease and 13 normal subjects (Figure I-26). These

studies confirmed that arterial blood oxygen saturation and carbon dioxide content at rest or during exercise were not predictive of impairment levels (Figure I-27).

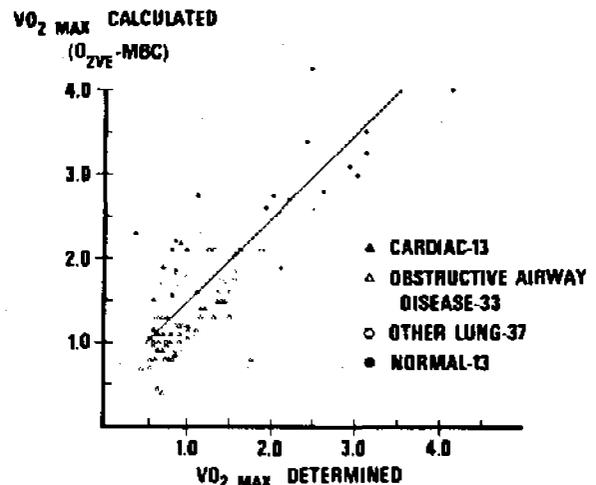


Figure I-26. Comparison of maximal oxygen consumption calculated from resting MVV and ventilatory equivalent during submaximal exercise to directly determined \dot{V}_{O_2} max.

Adapted from Armstrong, B. W., Workman, J. N., Hurt, H. H., Roemlich, W. R. Clinico-physiologic evaluation of physical working capacity in persons with pulmonary disease, Part II, *Am Rev Respir Dis*, 1966, 90:223-233.

This approach provides a useful method of estimating overall impairment of exercise capacity. However, certain limitations must be recognized. The presence of significant cardiovascular impairment may cause the actual maximal oxygen consumption to be lower than that estimated from Wright's equation. This was confirmed by Armstrong in several patients. Also, the ventilatory equivalent depends on the level of exercise at which it is measured. If measured at too low an energy output, voluntary hyperventilation can falsely elevate the ventilatory equivalent. When the anaerobic threshold is reached, ventilation begins to increase more rapidly relative to oxygen uptake, thereby increasing the ventilatory equivalent. At levels of exercise between these extremes, ventilation (\dot{V}) and oxygen consumption (\dot{V}_{O_2}) are related by the equation $\dot{V} = A \dot{V}_{O_2} + B$ where A and B are constants. Thus, \dot{V}/\dot{V}_{O_2} (ventilatory equivalent)

$$= A + \frac{B}{\dot{V}_{O_2}}$$

and the measured ventilatory equivalent decreases as exercise level (\dot{V}_{O_2}) increases. Finally, in patients with significant diffusion impairment, a sudden fall in end-pulmonary capillary blood

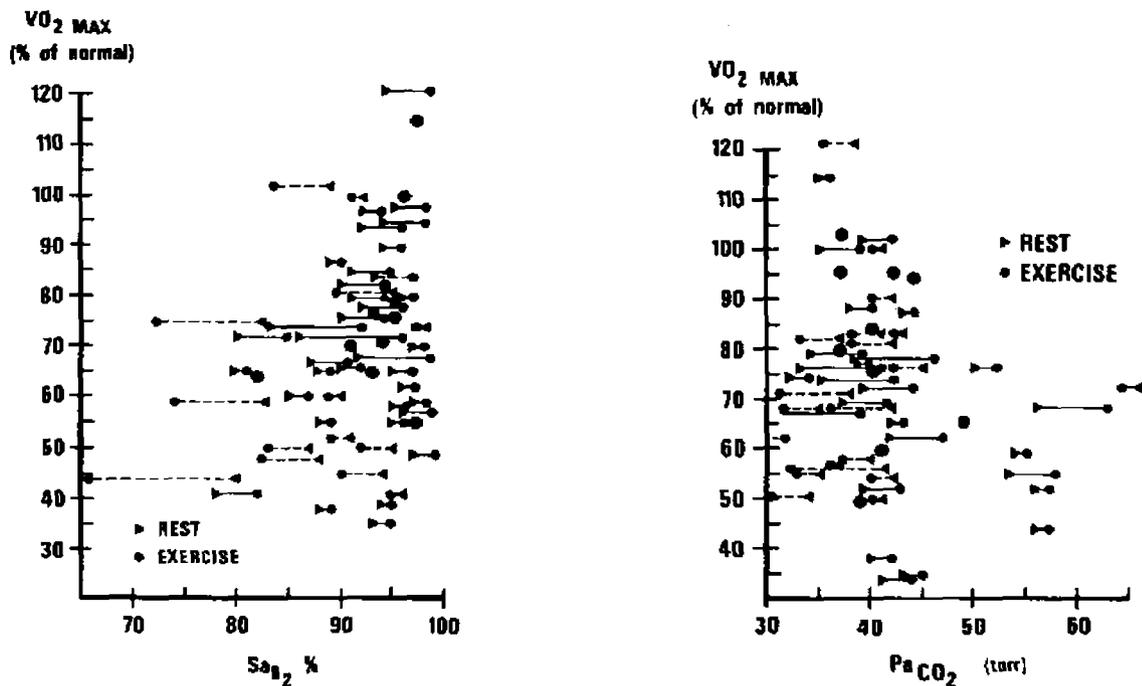


Figure I-27. Relationship of arterial blood oxygen saturation (Sa_{O_2}) and carbon dioxide tension (Pa_{CO_2}) to measured maximal oxygen uptake (\dot{V}_{O_2} , max).

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oxygen saturation may occur when a critical level of oxygen consumption is reached. This critical level is not necessarily predicted by the ventilatory equivalent at lower levels of exercise. Despite these limitations, the ventilatory equivalent has been found to be a useful measure in estimating impairment of exercise capacity (69).

RELATION OF EXERCISE CAPACITY TO WORKING ABILITY

If measured or predicted maximal oxygen consumption could be compared to the demands of work, the stress produced by that work could be estimated. The relative stress could then be used to decide whether a subject is disabled for a given job. Directly measuring oxygen consumption during normal working activity is difficult. Most studies have measured the relationship between oxygen consumption and heart rate in the laboratory, and then—by telemetry—measured heart rate during normal working activities. Such studies reveal that in most jobs, the level of energy expenditure is highly variable during the working period; brief periods of intense activity are followed by periods of lesser

activity. Walking mail carriers over 50-years-old and carrying 15 kg sacks of mail had an estimated oxygen consumption (averaged over the entire work period of approximately 2 hours) of 1.17 liters per minute. The most straining phase of their day's work required 1.45 liters per minute of oxygen consumption (56). The relative aerobic strain of the work (i.e., the oxygen consumption utilized, divided by the maximum oxygen consumption measured in the laboratory) was not significantly different between young and older men. The average relative aerobic strain for the working period was 54% for the men less than 35 years of age, and 55% for those greater than 50 years of age. However, the older men had a significantly lower maximal oxygen consumption than the younger men. This suggests that the older men were able to reduce the strain by pacing their work. The most straining phase of the work produced a stress of 68% for both the young and older men.

Among Columbian sugar cane loaders who load bundles weighing 1 to 2 kg on wagons, older workers showed a greater relative strain, using 35% of their maximum oxygen uptake averaged over an 8-hour period, compared to only 20%

in younger workers (72). However, productivity (as measured by the amount loaded) did not correlate with age, again suggesting that older workers are able to pace themselves and accomplish the same amount of work over an 8-hour day.

Astrand has shown that for high work rates, brief periods of work with brief rest periods produce very little elevation in blood lactate, whereas longer periods of work with longer rest periods produce high levels (Figure I-28)(5). This is probably attributable to utilization of muscle energy and oxygen stores to briefly achieve aerobic work rates above those usually carried out totally aerobically. When work stints are short, these stores are adequate to prevent anaerobic metabolism and lactate production. Stores are replenished during rest periods. When work stints are long, these stores are exhausted and lactate production ensues. The highest steady paced work, sustained by normal young men over a period of 8 hours, was approximately 35% of maximal oxygen consumption (49). Mail carriers over 50 years of age were able to tolerate short periods of oxygen consumption requiring 68% of maximal ability without undue fatigue. They sustained an average of 55% of maximal oxygen consumption for a 2-hour period. Clearly, work rate and pattern are crucial in determining the stress experienced by an individual with any limitation.

Several other factors are known to influence working capacity. Both physical size and level of habitual physical activity influence the total amount of work a subject can perform (77). The efficiency of transforming consumed oxygen into measurable external work performed varies between individuals and depends on work rate. As speed of walking was increased, net efficiency decreased in normal subjects (21). In older subjects, the net efficiency of work performed with the arms significantly decreased as the work rate was increased (55). For a given amount of external work, older subjects also consumed more oxygen than younger subjects, perhaps due to decreased coordination of movement. They also had a higher minute ventilation per unit of external work done (or oxygen consumed) than younger subjects (Figure I-29). A given level of external work may represent a greater physiologic strain for an older person, regardless of impairment.

Physiologic studies indicate that efficiency

may increase with training (31). Eight patients with emphysema, all of whom were hypoxemic at rest, were studied on a bicycle ergometer and then given 21 days of training on a treadmill. Training consisted of five 10 minute sessions per day (59). They were then restudied on the bicycle ergometer at the same level of exercise they had performed prior to the training. Exercise ability on the treadmill improved significantly; maximum tolerated speed increased from 1.35 miles/hour prior to training to 2.4 miles/hour after training. However, oxygen consumption, minute ventilation, ventilatory equivalent for oxygen, and arterial blood gases did not change between the pre- and post-training bicycle tests (Table I-72). The percent of total energy requirements obtained from anaerobic metabolism, estimated both by oxygen debt measurement and lactate levels during exercise, showed no change after training. The subjects' stride length on the treadmill increased significantly during the training period. This study suggests that training effect is not transferable between tasks and may be due to increased efficiency, specifically for the task performed during training. A similar study of 21 patients with obstructive lung disease and 8 control patients, included even more detailed physiologic monitoring (11). These subjects were studied before and

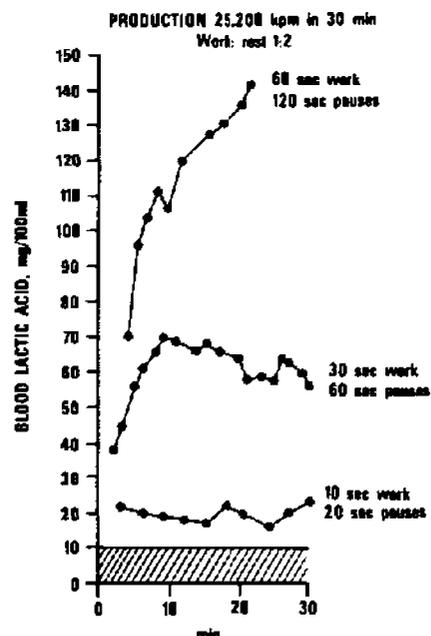


Figure I-28. Effect of pattern of work on lactate production.

From Textbook of Work Physiology by Astrand, P., Rodahl, K. Copyright 1970, McGraw-Hill Book Co. Used with permission of McGraw-Hill Book Company

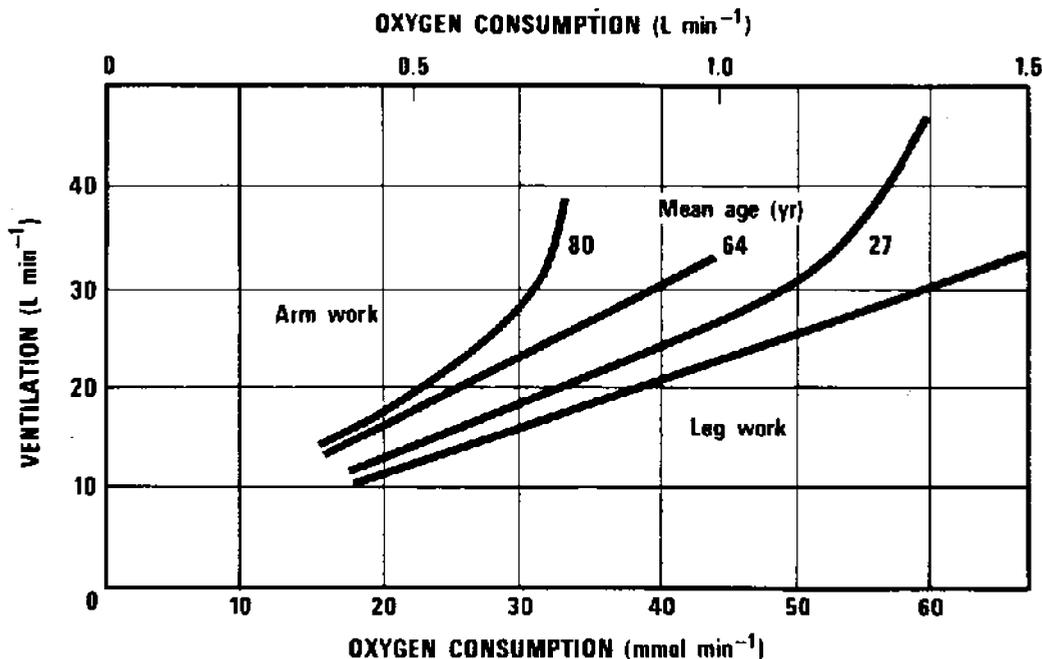


Figure 1-29. Ventilation and oxygen consumption during work using the arms for subjects of various ages.

Adapted by Cotes (1975) from Norris, A. H., Shock, N. W., Ylengst, M. J. Age differences in ventilatory and gas exchange responses to graded exercise in males. *J Gerontol*, 1955;10:145-155.

after an intensive 4 week rehabilitation training period consisting of daily exercise on a treadmill, rowing machine, bicycle and wall pulley; breathing exercises, postural drainage and medications; and psychological and vocational rehabilitation programs. After training, the FEV₁, peak flow, and forced expiratory flow over the mid portion of the vital capacity, maximum voluntary ventilation, residual volume, diffusing capacity, airway resistance, and dead space ventilation to tidal volume ratio did not change significantly in either the patient or control groups. Arterial blood gases, the alveolar-arterial oxygen gradient, the shunt fraction estimated by breathing 100% oxygen, and the ventilatory equivalent resting or during exercise, also showed no change. Likewise, no changes in cardiovascular function were noted. Heart rate, cardiac index, stroke volume, mean pulmonary artery pressure, and pulmonary vascular resistance were unchanged. However, the amount of total work performed on the treadmill by the patient group increased significantly. Oxygen consumption and minute ventilation at a given level of work on the treadmill decreased after training in the patient group but not in the controls. Neither the patients nor the controls showed any change in ventilation or oxygen consump-

tion on the bicycle after training. The authors, therefore, concluded that while training produced an increased ability to work, cardiopulmonary function had not changed. The increased ability to perform work on the treadmill was probably due to increased neuromuscular coordination and perhaps a decrease in the subject's sensitivity to the sensation of dyspnea as familiarity with the task increased. Clearly these studies have serious implications for attempting to relate exercise capacity in the laboratory to working ability on the job. As pointed out by Gaensler and Wright, conditions of work cannot easily be simulated in the laboratory, and prior training for a task clearly affects performance regardless of cardiopulmonary function (26).

Armstrong and co-workers found that none of 59 subjects who were working at the time of their study had an estimated maximal oxygen consumption less than 50% of the predicted normal value (3). Roemmich and co-workers applied the approach used by Armstrong to disability evaluation (62). They confirmed the Armstrong method produced reasonable estimates of maximum oxygen consumption for coal miners without significant impairment of gas exchange. They also estimated that an energy expenditure

Table I-72

PHYSIOLOGIC MEASUREMENTS IN PATIENTS WITH LUNG DISEASE BEFORE AND AFTER 21 DAYS OF TRAINING ON A TREADMILL

	Treadmill		Cycle Ergometer				
	Max. Speed (MPH)	Pulse (L/min)	\dot{V}_{O_2} (L/min) STPD	\dot{V}_E (L/min) BTPS	V.E.	PaO ₂ (Torr)	(a- \bar{v})O ₂ (Vol%)
Before training	1.35	91.3	.406	21.6	35	54	10.1
After training	2.40*	96.5	.412	20.5	34	57	11.7*
	*p<.05						

Adapted from Paez, P.N., Phillipson, E.A., Masangkay, M., Sproule, B.J. The physiologic basis of training patients with emphysema. *Am Rev Resp Dis*, 1967, 95:944-953.

\dot{V}_{O_2} = oxygen consumption per 100 kg-m of work

\dot{V}_E = ventilation

V.E. = ventilatory equivalent for oxygen

PaO₂ = arterial blood oxygen tension

(a- \bar{v})O₂ = arterial-mixed venous blood oxygen content difference

level of 7.5 times basal requirements would exceed the demands of the vast majority of jobs in the general labor market. Indeed, Jones et al. indicate energy demands for "mining and heavy industry" are approximately 7 to 8 times basal or 1.75-2.00 L/min of oxygen consumption (36). On direct exercise testing, Roemmich and co-workers found 26% of working coal miners had a capacity less than or equal to 1.75 liters per minute of oxygen consumption—confirming that a worker with this level of capacity can perform relatively strenuous work. By making certain assumptions, the FEV₁ expected to correspond to a capacity for maximal oxygen consumption of 7 to 8 times basal can be calculated from the Armstrong equation. Details are explained in Appendix IV. Values of FEV₁, which Roemmich and co-workers suggested as disability indicators in coal miners, were based on estimates of maximal oxygen consumption. This logical approach of relating objective measurements to overall functional and work (job) ability is useful but limited in application.

Perhaps more important than any of the technical factors already discussed are certain socioeconomic considerations. Haber studied the relationship between functional limitations as determined by ability to perform specific tasks (walking, lifting, writing, etc.) and overall disability as determined by a subject's actual work

history (32). At each level of functional limitation, a greater percentage of older subjects were disabled and a greater percentage of blue collar workers than white collar workers were disabled (Table I-73). Persons with a high school or college education were less disabled than those with lesser levels of education. Clearly, the type of work a subject is able to obtain has an important influence in determining disability levels associated with impairment.

Socioeconomic factors were also found to play a major role in influencing return to work following pneumonectomy for carcinoma (41). Fifty-seven percent of patients with severe lung disease (FEV₁ to FVC ratio of less than 50% or a vital capacity of less than 40% of predicted) returned to work compared to only 39% of those with less severe lung disease. When the type of work was considered, 26% of persons engaged in heavy labor activities or agriculture returned to work, whereas 73% of professionals were able to resume work. Diener and Burrows found that symptoms of dyspnea did not correlate with work status in 99 patients with obstructive lung disease who were followed for one year (20). However, a good prediction of work status could be obtained if job difficulty as well as cardio-pulmonary function was taken into consideration. Gilbert and co-workers found no difference in MVV, FEV₁ or arterial blood gases

Table 1-73
RELATIONSHIP BETWEEN FUNCTIONAL LIMITATION
(FOR SPECIFIC TASKS SUCH AS LIFTING) AND
DISABILITY DETERMINED FROM ACTUAL WORK HISTORY

Functional Limitation	% Severely Disabled								
	Age			Education				Job	
	18-44	45-54	55-64	<9 yr	9-11	12	College	Blue Collar	White Collar
None	14.6	17.5	23.4	29.5	13.7	15.2	8.5	27.6	14.7
Minor	25.6	23.9	40.0	} 39.0	} 30.9	} 22.3	} 24.3	} 49.9	} 31.5
Moderate	28.1	27.7	44.8						
Severe	43.2	39.3	52.9	} 64.6	} 59.4	} 41.6	} 43.1	} 70.8	} 52.6
Dependent	54.4	59.7	73.7						

Adapted from Haber, L.D. Disabling effects of chronic disease and impairment II. Functional capacity limitations. *J Chronic Dis*, 1973, 26:127-151.

between working and nonworking subjects with symptomatic obstructive lung disease (Figure I-30). All subjects who had an FEV₁ greater than 2 liters were working, but values of FEV₁ less than 2 liters had no predictive value for work status (28).

It has been amply demonstrated that factors other than objective impairment are vitally important in determining disability. Laboratory studies can provide estimates of functional capacity and even job demands, but must never be used as the sole criterion for disability evaluation.

RELATIONSHIP OF IMPAIRMENT TO CHEST RADIOGRAPH

Although abnormalities on chest radiograph are often present in persons with lung diseases associated with significant impairment, correspondence between function and radiologic findings is generally poor. A normal chest radiograph in no way eliminates the possibility of significant functional impairment. Forty percent of applicants for pulmonary disability benefits with normal chest radiographs had abnormal pulmonary function (12). Lindgren and co-workers also found poor correlation between pulmonary function and chest radiographs in 100 randomly selected claimants for disability due to lung disease (44). Of those without any objective impairment of pulmonary function, 50% showed some type of radiographic abnormality, while 62% of those with slight to moderate impairment

and 60% of those with severe pulmonary impairment had an abnormal chest radiograph. Radiographic abnormalities, including those suggestive of pulmonary hypertension, are not correlated with work status in patients with obstructive lung disease (20).

Lack of correlation between radiographic findings and function has also been demonstrated for occupational diseases such as simple coal workers' pneumoconiosis (51). Gaensler and co-workers demonstrated a significant correlation of restrictive impairment and radiographic abnormality in workers with exposure to asbestos but not in those with other dust exposures (24). For individuals, correspondence of function and radiologic findings was poor. Persons whose radiograph was classified as 0/0 or 0/1 by the UICC/Cincinnati classification system (i.e., showing little or no evidence of pneumoconiosis) had vital capacities ranging from 50% to 98% of predicted. The range for diffusing capacity in these same subjects was 49% to 128% of predicted. In persons with very abnormal chest radiographs (categories 3/3 or 3/4), the vital capacity ranged from 38% to 72% of predicted and the diffusing capacity from 18% to 86% of predicted. The authors concluded that chest radiographs are of no use in predicting impairment in individuals and thus of no use in this phase of disability evaluation. Chest radiographs are, however, important in establishing a diagnosis and may be helpful in relating pulmonary impairment to occupational exposure.

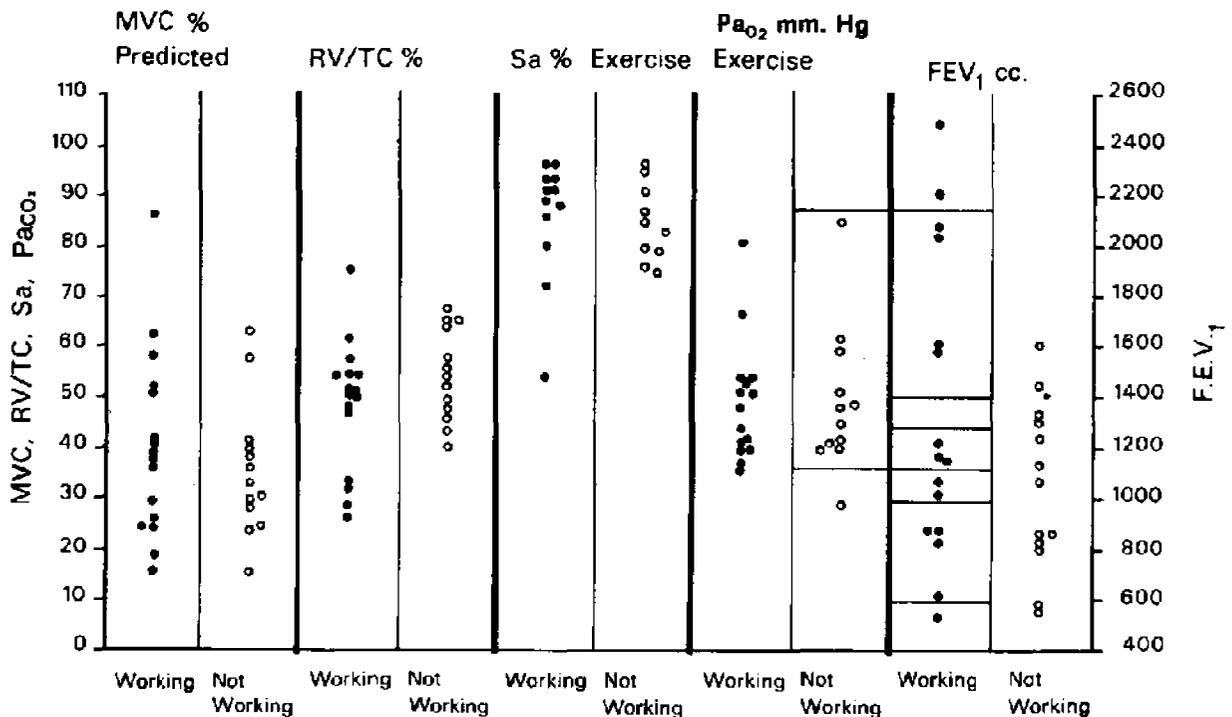


Figure I-30. Relationship of various parameters of pulmonary function and working status.

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SUMMARY AND RECOMMENDATIONS

Impairment is difficult to quantitate because of the wide range of "normal" function, and the [usual] lack of information about individual functional capacity prior to the onset of illness. Remaining functional capacity can be determined more accurately than amount of function lost. The physiologic stress caused by an activity is directly proportional to the fraction of an individual's remaining maximal capacity required by the demands of that activity. A given percentage reduction in function from "normal" is more incapacitating for an older individual. The remaining function is lower than that of a younger person with the same percentage loss in function, and the demand for function (e.g., ventilation) to perform at a given level of work is greater in older subjects. Thus, disability evaluation should focus on determining the remaining ability to function and its relation to the demands of the work to be performed.

Work or job demands are difficult to quan-

titate due to individual factors of work pattern and rate and prior training. Also, the ability to tolerate sensations of breathlessness varies between individuals. Nevertheless, an estimate of job demands is essential in determining whether an individual with a given level of function is disabled.

The final determination of disability must take into account socioeconomic and psychological factors such as education, past work experience, job availability, and motivation, as well as remaining pulmonary function. Because of the complex interaction of these factors, no level of function defined by medical testing can accurately separate those who are unable to perform a certain job from those who are. Appendix I contains a summary of criteria for disability evaluation currently in use or suggested by authorities. Appendix II provides specific values or ratings for Federal programs. More complex measurements than those indicated in Appendix I have not been shown to improve the accuracy of predicting the ability to work. Exercise testing

may add useful information when more than one organ system is impaired and in cases with borderline pulmonary impairment. It is probably not necessary as a screening procedure in disability evaluation if spirometry, resting blood gases, and in some cases, diffusing capacity are performed. It is valuable as a research tool.

Appendix III compares pulmonary function values, which define severe impairment or disability, for a male 70" tall under six schemes of evaluation. Values for the "degree of pulmonary disability" (DPD) from Wilson's equations (81) and estimated maximal oxygen consumption according to Armstrong and co-workers (3) have been calculated by making certain assumptions when all parameters in the prediction equations are not specified in the evaluation scheme. Use of these assumptions (noted in Appendix III), even if not completely valid, allows a useful comparison of the various schemes.

If a fixed percentage of normal predicted values is used to determine disability, older subjects are clearly disadvantaged. The estimated $\dot{V}O_2$ max declines and the DPD increases with age. With obstructive impairment, an FEV₁ of 1.8 L is associated with an estimated maximal oxygen consumption of approximately 1.8 L/min and a DPD of 250-275, depending on age. This is a level of impairment which may be disabling for work requiring moderate physical exertion. This FEV₁ is approximately 55% of predicted for a 60-year-old (70" tall) male and 49% for a 40-year-old. Thus, setting a guideline for disability due to obstructive impairment at 55% of the predicted FEV₁ for 60-year-olds, and applying this value to all younger applicants is reasonable. This assumes no severe "gas exchange" impairment is present. For restrictive (interstitial) impairment, values for FVC and $D_{L(SB)}$ of 55% of those predicted for a 60-year-old result in DPD scores of approximately 250-275, depending on age. Estimated $\dot{V}O_2$ max values are not as useful because of the arbitrary choice made for $\dot{V}E_{O_2}$ in the calculations, but do suggest that this level of impairment would be disabling for moderately strenuous work.

This author recommends that values of pulmonary function, equal to or less than 55% of the predicted level at age 60 years, be used as general guidelines for possible total disability due to pulmonary impairment. Predicted levels

should be those of one of the recent surveys, and separate predictions for women and blacks should be used.

Arterial blood gas tensions are generally difficult to interpret as an index of impairment. However a Pa_{O_2} at or below 55 to 60 torr at sea level (with $Pa_{CO_2} = 40 \pm 2$ torr) should be considered suggestive of disabling impairment. If not consistent with all other findings, arterial blood gases should be measured during steady state exercise of mild intensity (e.g., $\dot{V}O_2 = 0.75 - 1.0$ L/Min). Any further drop in Pa_{CO_2} should be considered confirmation of severe impairment. A Pa_{CO_2} equal to or greater than 50 torr at sea level should also be considered evidence of severe impairment.

These recommendations are presented as guidelines for disability evaluation. They cannot be used to define disability nor substitute for the judgment of experienced physicians and claims adjudicators in determining the capability for work of a given individual.

RESEARCH NEEDS

It is clear that research is needed in several areas in disability evaluation. Better predicted values for normal levels of pulmonary function are needed, especially in non-Caucasians. The influence of subject cooperation on pulmonary function testing in disability applicants needs further study. More accurate predictions of the demands of work and the influence of work rate and training on the ability to perform a given task are needed. An area which has received essentially no study is that of psychological factors related to the perception of the sensation of dyspnea. Of these, the quantitation of the physical demands of contemporary jobs is probably the most urgently needed "technical" research. A better understanding of the interaction of psychological and social factors with physical impairment would probably have the most significant impact on the overall evaluation of disability.

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Appendix I
SUMMARY OF CRITERIA FOR SEVERE IMPAIRMENT OR
TOTAL DISABILITY DUE TO PULMONARY DISEASE

	“Obstructive” Impairment	“Restrictive” (Interstitial) Impairment
AMA⁽²⁾ (60-90% impairment)	FVC, FEV ₁ , and MVV < 55% predicted (at least 2 should be measured). Note: “obstructed” and “restricted” not distinguished, blood gas values placed under “restriction” for convenience	Arterial blood oxygen saturation usually less than 88% at rest and after exercise (SaO ₂ = 88% corresponds to approximately PaO ₂ = 54 torr at 37°C and pH = 7.40
Gaensler & Wright⁽³⁾ (severe impairment)	FEV ₁ /FVC < .40 MVV ≤ 45% predicted (if done)	FVC ≤ 50% predicted or D _{L(SB)} ≤ 40% predicted SaO ₂ < 92% at rest and decreasing with exercise (SaO ₂ = 92% corresponds to approximately PaO ₂ = 63 torr at 37°C and pH = 7.40)
Wilson, et al.⁽⁴⁾	Degree of pulmonary disability (DPD) calculated from formula including MVV, FEV ₁ , age and FVC (DPD = 300 if dyspnea with slight exercise; DPD = 200 if mild dyspnea at rest)	DPD computed from formula including MVV, D _{L(SB)} , FEV ₁ , and age Same interpretation as “obstructive”
Veterans Administration⁽⁸⁾	Rating of impairment in earning capacity based on comparison of symptoms and examination results with rating schedule description. Total disability may be assigned even if rating less than 100% when person is unable to secure or follow a substantially gainful occupation provided that a single disability of ≥ 60% rating is present (or combined disabilities of ≥ 70% rating). See Appendix II(a)	
Social Security⁽¹⁾ (total disability)	FEV ₁ and MVV values based on height only (see Appendix II(a))	FVC values based on height [see Appendix II(b)] and D _{L(SB)} < 30% predicted or < 9 ml/mmHg/min or arterial blood oxygen saturation ≤ 87 (adjusted up if arterial blood carbon dioxide tension is below 40 torr) Note: SaO ₂ ± 87 corresponds to approximately PaO ₂ = 52 torr at 37°C and pH = 7.40
Social Security Black Lung Benefits^{** (5)}	FEV ₁ and MVV values based on height (see Appendix II(a))*	PaCO ₂ ≤ 55 torr (adjusted up if PaO ₂ < 40 torr)

Appendix I
SUMMARY OF CRITERIA FOR SEVERE IMPAIRMENT OR
TOTAL DISABILITY DUE TO PULMONARY DISEASE

	"Obstructive" Impairment	"Restrictive" (Interstitial) Impairment
Social Security Black Lung Interim*** ⁽⁶⁾	FEV ₁ and MVV values based on height (see Appendix II(a))*	PaCO ₂ ≤ 55 torr (adjusted upward if PaO ₂ < 40 torr)
Department of Labor Proposed Black Lung Benefits ⁽²⁾	FEV ₁ ≤ 60% predicted for age, height, and sex (based on Knudson <i>et al.</i> , 1976) and MVV ≤ 60% of the 40 × predicted FEV ₁ *	PaCO ₂ ≤ 60 torr (PaCO ₂ = 40-45 torr PaO ₂ adjusted upward if PaCO ₂ < 40 torr) or PaCO ₂ < 45 torr with any PaO ₂

***"Obstructive" and "restricted" not distinguished, blood gas values placed under "restriction" for convenience.

**These standards have also been used by Department of Labor to administer this program since 1973.

***These standards (with a revision of PaO₂ to 60 torr and addition of PaCO₂ 45 torr with any PaO₂ are being used to administer the program until permanent revised standards (under the Black Lung Benefits Reform Act of 1977) are adopted.

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5. 20 Code of Federal Regulations, Subpart D—Total Disability of Death Due to Pneumoconiosis, 410.426.
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7. Standards for determining coal miner's total disability or death due to pneumoconiosis. Federal Register, 45(42), Friday, February 29, 1980. 13678-13712.
8. 38 Code of Federal Regulations Pension Bonuses & Veterans' Relief, Revised as of July 1977.

Appendix II(a)
SOCIAL SECURITY
OBSTRUCTIVE IMPAIRMENT

Chronic obstructive airway disease (chronic bronchitis, chronic asthmatic bronchitis or pulmonary emphysema with or without abnormal x-ray findings). With: Spirometric evidence of airway obstruction demonstrated by MVV and FEV₁ both equal to, or less than, the values specified in Table I-70, corresponding to the applicant's height.

Height (inches)	MVV (MBC) equal to or less than L./Min.	and	FEV ₁ equal to or less than L.
57 or less	32		1.0
58	33		1.0
59	34		1.0
60	35		1.1
61	36		1.1
62	37		1.1
63	38		1.1
64	39		1.2
65	40		1.2
66	41		1.2
67	42		1.3
68	43		1.3
69	44		1.3
70	45		1.4
71	46		1.4
72	47		1.4
73 or more	48		1.4

Appendix II(a)
SOCIAL SECURITY
BLACK LUNG BENEFITS

Pneumoconiosis shall be found disabling if it is established that the miner has (or had) a respiratory impairment because of pneumoconiosis demonstrated on the basis of a ventilatory study in which the maximum voluntary ventilation (MVV) or maximum breathing capacity (MBC), and 1-second forced expiratory volume (FEV₁) are equal to or less than the values specified in the following table or by a medically equivalent test:

Height (inches)	MVV (MBC) equal to or less than L./Min.	and	FEV ₁ equal to or less than L.
57 or less	52		1.4
58	53		1.4
59	54		1.4
60	55		1.5
61	56		1.5
62	57		1.5
63	58		1.5
64	59		1.6
65	60		1.6
66	61		1.6
67	62		1.7
68	63		1.7
69	64		1.8
70	65		1.8
71	66		1.8
72	67		1.9
73 or more	68		1.9

Arterial blood gas values are the same as those for "Interim" Social Security Black Lung Benefits.

Appendix II(a)
SOCIAL SECURITY
INTERIM BLACK LUNG BENEFITS

In the case of a miner employed for at least 15 years in underground or comparable coal mine employment, ventilatory studies establish the presence of a chronic respiratory or pulmonary disease as demonstrated by values which are equal to or less than the values specified in the following table:

Height (inches)	Equal to or less than	
	FEV ₁	MVV
67" or less	2.3	92
68"	2.4	96
69"	2.4	96
70"	2.5	100
71"	2.6	104
72"	2.6	104
73" or more; and	2.7	108

Arterial oxygen tension at rest (sitting or standing) or during exercise and simultaneously determined arterial P_{CO_2} equal to, or less than, the values specified in the following table:

Arterial P_{CO_2} (mm. Hg)	and	Arterial P_{CO_2} equal to or less than (mm. Hg.)
30 or below		65
31		64
32		63
33		62
34		61
35		60
36		59
37		58
38		57
39		56
40 or above		55

Appendix II(a)
DEPARTMENT OF LABOR
INTERIM BLACK LUNG BENEFITS

Spirometric values are the same as Social Security Interim Black Lung Benefits.

Arterial pCO_2 (mm. Hg)	and	Arterial pO_2 equal to or less than (mm. Hg.)
30 or below		70
31		69
32		68
33		67
34		66
35		65
36		64
37		63
38		62
39		61
40-45		60
Above 45		Any value

Appendix II(a)
DEPARTMENT OF LABOR
BLACK LUNG BENEFIT STANDARDS

A miner who meets the following medical specifications shall be found to be totally disabled, in the absence of rebutting evidence, if the values specified in the following table are met.

For arterial blood-gas studies performed at test sites up to 4,000 feet above sea level:

Arterial pCO ₂ (mm. Hg)	Arterial pO ₂ equal to or less than (mm. Hg.)
25 or below	75
26	74
27	73
28	72
29	71
30	70
31	69
32	68
33	67
34	66
35	65
36	64
37	63
38	62
39	61
40-45	60
Above 45	Any value

For arterial blood-gas studies performed at test sites between 4,000 and 6,000 feet above sea level.

1. Any pO₂ value which is equal to or below 60 mm. Hg., or
2. Any pCO₂ value which is equal to or above 42 mm. Hg.

Appendix II(a)
VETERANS ADMINISTRATION
RATING SCHEDULE FOR THE RESPIRATORY SYSTEM
Selected Conditions

	Rating
Bronchitis, chronic	
Pronounced; with copious productive cough and dyspnea at rest; pulmonary dyspnea at rest; pulmonary function testing showing a severe degree of chronic airway obstruction; with symptoms of associated severe emphysema or cyanosis and findings of right-sided heart involvement.....	100
Severe; with severe productive cough and dyspnea on slight exertion and pulmonary function tests indicative of severe ventilatory impairment.....	60
Moderately severe; persistent cough at intervals throughout the day, considerable expectoration, considerable dyspnea on exercise, rales throughout chest, beginning chronic airway obstruction.....	30
Moderate; considerable night or morning cough, slight dyspnea on exercise, scattered bilateral rales.....	10
Mild; slight cough, no dyspnea, few rales.....	0
Emphysema, pulmonary	
Pronounced; intractable and totally incapacitating; with dyspnea at rest, or marked dyspnea and cyanosis on mild exertion; severity of emphysema confirmed by chest X-rays and pulmonary function tests.....	100
Severe; exertional dyspnea sufficient to prevent climbing one flight of steps or walking one block without stopping; ventilatory impairment of severe degree confirmed by pulmonary function tests with marked impairment of health.....	60
Moderate; with moderate dyspnea occurring after climbing one flight of steps or walking more than one block on level surface; pulmonary function tests consistent with findings of moderate emphysema.....	30
Mild; with evidence of ventilatory impairment on pulmonary function tests and/or definite dyspnea on prolonged exertion.....	10
Anthracosis (Black Lung Disease)	
Silicosis	
Pneumoconiosis, unspecified	
Pronounced; with extent of lesions comparable to far advanced pulmonary tuberculosis or pulmonary function tests confirming a markedly severe degree of ventilatory deficit; with dyspnea at rest and other evidence of severe impairment of bodily vigor producing total incapacity.....	100
Severe; extensive fibrosis, severe dyspnea on slight exertion with corresponding ventilatory deficit confirmed by pulmonary function tests with marked impairment of health.....	60
Moderate; with considerable pulmonary fibrosis and moderate dyspnea on slight exertion, confirmed by pulmonary function tests.....	30
Definitely symptomatic with pulmonary fibrosis and moderate dyspnea on extended exertion.....	10

Appendix II(b)
SOCIAL SECURITY
RESTRICTIVE (INTERSTITIAL) IMPAIRMENT

Diffuse pulmonary fibrosis (sarcoidosis, Hamman-Rich Syndrome, idiopathic interstitial fibrosis, and similar diffuse fibroses substantiated by chest x-ray or tissue diagnosis. This category does not include cases of bronchitis or emphysema with incidental scarring or scattered parenchymal fibrosis on x-ray). With:

- A. Total vital capacity equal to, or less than, values specified in Table below corresponding to the applicant's height.

Height (inches)	V. C. equal to or less than (L.)
57 or less	1.2
58	1.3
59	1.3
60	1.4
61	1.4
62	1.5
63	1.5
64	1.6
65	1.6
66	1.7
67	1.7
68	1.8
69	1.8
70	1.9
71	1.9
72	2.0
73 or more	2.0

Appendix II(b)
SOCIAL SECURITY
RESTRICTIVE (INTERSTITIAL) IMPAIRMENT (continued)

B. Diffusing capacity of the lungs for carbon monoxide less than 6 ml./mm. Hg./min. (steady-state methods) or less than 9 ml./mm. Hg./min. (single-breath methods) or less than 30 percent of predicted normal. (All methods—actual values and predicted normal for the method used should be reported);

C. Arterial oxygen saturation at rest and simultaneously determined arterial pCO₂ equal to, or less than, the values specified in Table below.

Arterial pCO ₂	and	Arterial O ₂ saturation equal to or less than (%)
30 mm. Hg. or below		93
31 mm. Hg.		93
32 mm. Hg.		92
33 mm. Hg.		92
34 mm. Hg.		91
35 mm. Hg.		91
36 mm. Hg.		90
37 mm. Hg.		89
38 mm. Hg.		88
39 mm. Hg.		88
40 mm. Hg. or above		87

Appendix III(a)
VALUES FOR SCHEMES DESCRIBED IN APPENDIX I
FOR MALE OF HEIGHT 70" (178 cm) WITH "OBSTRUCTIVE" IMPAIRMENT

	Age (yrs)	40	50	60
<i>Social Security</i>	FEV ₁ (L)	1.4(35%)*	1.4(38%)	1.4(41%)
Estimated \dot{V}_{O_2} max**	(L/min)	1.58	1.58	1.58
Estimated DPD***		240	220	200
<i>AMA</i>	FEV ₁ (L)	2.18(55%)*	2.04(55%)	1.89(55%)
Estimated \dot{V}_{O_2} max**	(L/min)	2.05	2.02	1.95
Estimated DPD***		315	290	275
<i>Gaensler & Wright</i>	FEV ₁ + (L)	1.79(45%)*	1.67(45%)	1.54(45%)
Estimated \dot{V}_{O_2} max**	(L/min)	1.90	1.84	1.78
Estimated DPD††		250	275	200
<i>Black Lung Interim</i>	FEV ₁ (L)	2.5(63%)*	2.5(68%)	2.5(73%)
Estimated \dot{V}_{O_2} max**	(L/min)	2.24	2.24	2.24
Estimated DPD***		360	340	325
<i>Department of Labor Black Lung Standards</i>	FEV ₁ (L)	2.38(60%)*	2.22(60%)	2.06(60%)
Estimated \dot{V}_{O_2} max**	(L/min)	2.19	2.11	2.03
Estimated DPD***		350	310	260

* () = % predicted based on Knudson, et al. (1976).

**From equation of Armstrong, et al. (1966) assuming $VE_{O_2} = 25$, $MVV = 40 FEV_1$ if not specified.

***From equation of Wilson, et al. (1964), if not specified assumed $FVC = \frac{FEV_1}{.55}$.

†Approximately equivalent to $MVV < 45\%$ predicted.

††FVC assumed = $\frac{FEV_1}{.40}$.

Appendix III(b)
VALUES FOR SCHEMES DESCRIBED IN APPENDIX I
FOR MALE OF HEIGHT 70" (178 cm) WITH
"RESTRICTIVE" (INTERSTITIAL) IMPAIRMENT

	Age (yrs)	40	50	60
Social Security				
FVC (L)		1.9(38%)*	1.9(41%)	1.9(43%)
$D_{L(SB)}$ (ml/mmHg/min)		9.72(30%)*	9.12(30%)	8.52(30%)
Estimated \dot{V}_{O_2} max**	(L/min)	1.11	1.11	1.11
Estimated DPD†		222	200	178
If $D_{L(SB)}$ reduced in proportion to FVC				
$D_{L(SB)}$ (ml/mmHg/min)		12.3(38%)*	12.5(41%)	12.2(43%)
Estimated \dot{V}_{O_2} max***	(L/min)	1.11	1.11	1.11
Estimated DPD†		239	222	202
AMA				
FVC (L)		2.72(55%)*	2.56(55%)	2.40(55%)
$D_{L(SB)}$ (ml/mmHg/min)		17.82(55%)*	16.72(55%)	15.62(55%)
Estimated \dot{V}_{O_2} max**	(L/min)††	1.65	1.58	1.52
Estimated DPD		326	291	255
Gaensler & Wright				
FVC (L)		2.48(50%)*	2.33(50%)	2.18(50%)
$D_{L(SB)}$ (ml/mmHg/min)		13.0(40%)**	12.2(40%)	11.4(40%)
Estimated \dot{V}_{O_2} max***	(L/min)	1.33	1.27	1.21
Estimated DPD		279	246	214
If $D_{L(SB)}$ reduced only to 50% predicted				
$D_{L(SB)}$ (ml/mmHg/min)		16.2(50%)**	15.2(50%)	14.2(50%)
Estimated \dot{V}_{O_2} max††	(L/min)	1.55	1.49	1.44
Estimated DPD		300	266	235

* () = % predicted based on Knudson, et al. (1976).

**Normal predictions from Cotes (1975).

***From equation of Armstrong, et al. (1966) VE_{O_2} assumed = 40.

†From equation of Wilson, et al. (1968), FEV_1 assumed = .8 FVC, MVV assumed = 40 FEV_1 .

††Assumed to be reduced in proportion to FVC.

Appendix IV
CALCULATION OF FEV₁ EXPECTED TO CORRESPOND TO
A GIVEN MAXIMAL OXYGEN CONSUMPTION CAPACITY

Armstrong equation for maximal oxygen consumption (ref 2):

$$V_{O_2} \text{ (L/min)} = 2.14 + .012 \text{ MVV} - .044 \text{ VE}_{O_2}$$

where $V_{O_{2max}}$ = predicted voluntary ventilation

VE_{O_2} = ventilatory equivalent for oxygen (oxygen consumption divided by minute ventilation)

For a man aged 50 years and 70" tall assume basal V_{O_2} of .250 L/min. To estimate FEV₁ corresponding to maximal oxygen consumption capacity of 7.3 × basal:

1) $(7.3)(.250) = 2.14 + .012 \text{ MVV} - .044 \text{ VE}_{O_2}$

2) if O_{2vc} assumed to be 25 (i.e. normal)

3) $2.825 = 2.14 + .012 \text{ MVV} - 1.10$

4) $.012 \text{ MVV} = .795$

5) $\text{MVV} = 65.4 \text{ L}$

6) if $\text{MVV assumed} = 36 \times \text{FEV}_1$, then $\text{FEV}_1 = 1.8 \text{ L}$

Thus Roemmich and coworkers estimated that a 50 year old 70" tall man with an FEV₁ = 1.82 would have a maximal oxygen consumption of 1.83 L/min or 7.3 × basal.

Adapted from Roemmich et al. (1972).

Addendum to Chapter

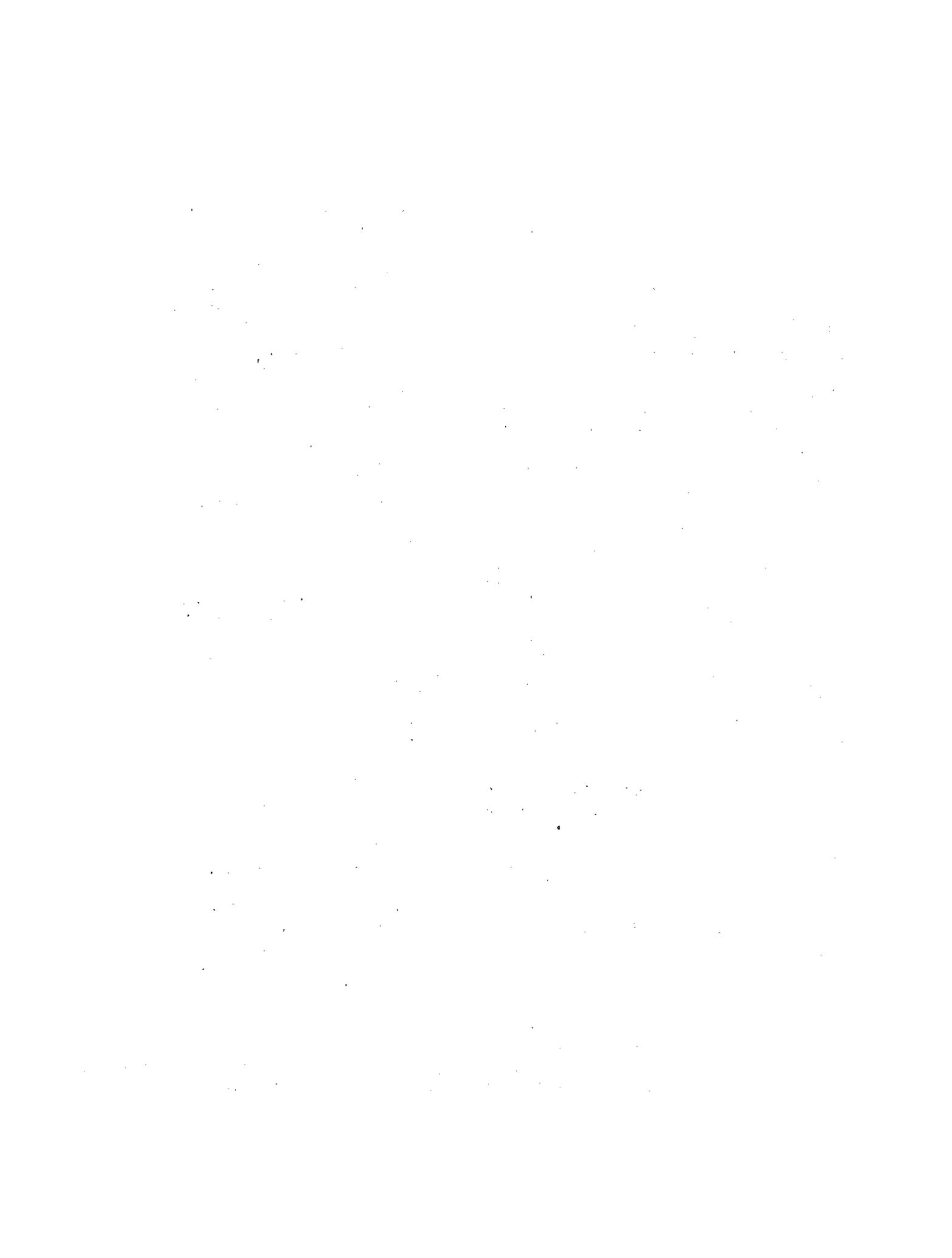
This chapter was submitted in December 1979. More recent sources should be consulted for current governmental agency regulations concerning disability due to respiratory impairment. Recent general references on topics covered in this chapter are listed below.

B. Boehlecke

1. Miller, William F. and Scacci, Robert. Pulmonary Function Assessment for Determination of Pulmonary Impairment and Disability Evaluation. Clinics in Chest Medicine 2(3):327-341, 1981.

2. Pulmonary Function Testing Guidelines and Controversies: Equipment, Methods, and Normal Values. N.Y. Academic Press, 1982 ed. Jack Clausen
3. Clinical Exercise Testing. Philadelphia, Saunders 1982 N.L. Jones and E.J. Moran Campbell.

SECTION II
PNEUMOCONIOSES



SILICOSIS

John M. Peters

INTRODUCTION

In 1556 Agricola wrote in *De re metallica*, "It remains for me to speak of the ailments and accidents of mines, and of the methods by which we can guard against them, for we should always devote more care to maintaining our health, than we may freely perform our bodily functions, than to making profits." This advice is no less true today and underlines one of the reasons silicosis is prevalent. While our medical, engineering, epidemiologic, and toxicologic knowledge concerning silica and silicosis is incomplete, it is sufficient to render silicosis a rare disease where appropriate action is taken to reduce workplace exposure to the many dusts containing silica (SiO_2). Further research will undoubtedly refine our knowledge of: silica's mechanism of action; its interaction with other environmental agents (such as cigarette smoking); its genetic predisposition; its pathophysiology; and its dose-response relationships. But the elimination of silicosis, while relying on technology, will be sociological. How do we achieve "safe" dust levels in the workplaces in which exposure to silica is taking place? Regulation and enforcement are obviously important, but what are the best laws? The best economic incentives for control? The best political solutions? The best technical solutions? And what research needs to be conducted to provide "policy makers" with the right information to make policy compatible with both occupational health and production? In large part, this chapter is devoted to considering the scientific issues inextricably bound with policy issues which must be addressed before silicosis is a thing of the past.

DEFINITION

Silicosis is a fibrotic disease of the lungs produced by the inhalation and deposition of dust containing silicon dioxide or silica (SiO_2). It can take the acute form under conditions of

intense exposure but usually takes the chronic form, requiring several to many years to develop. It has frequently been associated with tuberculosis (silicotuberculosis) and other mycobacteria which synergistically increase its pathogenicity. The interested reader is referred to several useful sources (19)(22)(33). Much of the following material is derived from these sources.

Chronic Manifestations

Chronic reactions, occurring over 20 to 45 years, usually involve exposure to dusts containing a relatively small proportion of quartz (30% or less). Lesions are usually nodular and are likely to be more prominent in the upper lobes. In this *simple* stage of silicosis, nodules are usually small (5mm or less). Normally this stage has little effect on pulmonary function.

Complicated silicosis (progressive massive fibrosis) also usually develops in the upper lobes. In this case fibrotic nodules coalesce and encompass blood vessels and airways. Function may be severely compromised under these conditions. In the past, tuberculosis was a common accompaniment of this condition.

Caplan's syndrome was first described in coal miners with rheumatoid arthritis (3). It was subsequently found in other mining occupations. Its most characteristic feature is larger, more rapidly developing nodules than those seen in simple silicosis. An increased prevalence of progressive massive fibrosis is seen in these individuals.

Acute and Accelerated Silicosis

Very high exposure to silica can result in acute silicosis. This disease may appear one to three years after the onset of exposure. The distinguishing feature of acute silicosis is intra-alveolar deposits (similar to those seen with alveolar proteinosis), appropriately termed "silico-proteinosis." Additionally, in contrast to the nodular fibrosis seen in the chronic form, diffuse

interstitial fibrosis is found. Silicosis developing in less than 10 years has been described most often in sandblasters. In these cases, massive fibrosis is likely to develop and locate in the middle and lower lobes. (See Acute Silicosis subsection, page 239).

CAUSATIVE AGENTS

Silicon dioxide or silica (SiO_2), the agent responsible for silicosis, occurs in three different mineralogical forms. These are quartz, cristobalite, and tridymite. Quartz has hexagonal crystals; cristobalite, cubic crystals; and tridymite, hexagonal. The noncrystalline forms of silica (amorphous silica) are considered to have little fibrotic potential. Heating, however, can change their structure into crystalline form.

The primary source of silica is quartz. Quartz is a mineral found in nearly all mineral deposits and is an important component of common rocks such as granite and sandstone. This is the principle reason workers are exposed to it in various occupations. Sand contains large amounts of quartz and is used in the glass and pottery industry as well as in brick, mortar, and abrasives production. In finely pulverized form (silica flour), it is added to soaps, paints, and porcelains. Since crystalline silica occurs in various colors, these materials find use as gems or for other decorative purposes.

Cristobalite and tridymite are two minerals that usually occur together, a major source being volcanic rock in California, Colorado, and Mexico (31). These two minerals can also be man-made by heating silica (either crystalline or amorphous) to high temperatures. This process occurs in calcining diatomaceous earth; resulting products find use in insulation, filters, and furnace linings.

Flints contain free silica and have been used for centuries because of their hardness and heat resistance.

OCCUPATIONS AND INDUSTRIES INVOLVED

Abrasives	Nonmetallic mining and milling
Abrasive blasting	Plastic manufacturing
Boiler scaling	Pottery making
Cement production workers	Refractories
Ceramics	Road working
Coal mining and milling	Rubber manufacturing

Fillers (paints, rubber, etc.)	Sandblasting
Foundry work (ferrous and non-ferrous)	Scouring soap manufacturing
Glass manufacture	Tile and clay production
Insulation production and installation	Tunneling
Metal mining and milling	Vitreous enameling
Mining, quarrying and tunneling	

EPIDEMIOLOGY

One definition of epidemiology is the study of the distribution and determinants of disease. The classical process consists of examining a series of variables to ascertain causation. Variables usually include age, sex, race, socioeconomic status, ethnicity, religion, etc. Since it is known that silica causes silicosis, and that a certain level of exposure produces disease in humans regardless of sex, age, or race, this section will deal primarily with evidence relating dose to response in human beings.

There are several major difficulties involved in attempting to do this. They fall primarily into three categories:

- 1) difficulties in the accurate determination of dose,
- 2) difficulties in the accurate determination of health effects (or disease) and,
- 3) difficulties in dealing with competing variables (such as cigarette smoking and host susceptibility).

These three problems will be generically discussed. Available literature will then be reviewed, and the final segment of this chapter will summarize the current state of knowledge and questions that must be addressed by further research.

Dose

It is obviously important to know how the silica particle exerts its toxic effect. Is it related to the number of particles? To the size of the particles? To the concentrations? Any attempt to make meaningful exposure measurements should involve consideration of these factors.

There is another set of questions relating to the deposition and clearance of particles. What are the characteristics of particles that penetrate

to the large airways? The small airways? The alveoli? What role do host factors, such as the immune system or anatomy, play? Are there special characteristics about particles that are cleared versus particles that destroy macrophages?

The measurement of airborne dust in the workplace must bear some general relationship to the toxic amount of silica delivered to the lung, but there are clearly important questions that can be raised about this relationship. We can accurately measure silica dust levels, but how do we assess the chronic, long-term effects of "low-level" exposure to silica? Assuming workplace exposure relates somehow to delivered dose, we still have the difficulty of ascertaining a working-lifetime exposure to silica. Over the years actual measurement techniques have changed, work processes have changed and environmental hygiene has changed.

Personal habits also affect exposure. Two persons working the same jobs may position themselves differently, may use the local exhaust ventilation differently, and may take their breaks in different places. All of these sorts of personal work characteristics make area sampling highly suspect in representing true exposure. Personal sampling techniques are obviously needed. Ideally we would like a personal sampling result for every worker every day. This is, of course, not possible. Even if it were, accurate personal sampling techniques have only been available for the past few years and in the case of silica, we need exposure data for the previous 20 to 40 years in order to determine lifetime exposure levels. Other components of dust besides silica may be important. It is uncommon in industries in which silica exposures occur for the exposure to be purely to SiO_2 . Other materials are present in mines, foundries, quarries, construction sites, etc. These other exposures may be important either by directly influencing the toxicity of silica or by exerting effects on the respiratory system themselves. This raises the question of whether a certain amount of exposure to silica in a foundry produces the same effect as the same amount of silica in a granite shed.

Response—Health Effects

Silica has the potential to damage the lung. There are several ways to monitor silica-induced lung damage. First, on an individual basis, detectable effects on both chest x-ray and pulmo-

nary function occur prior to frank clinical symptoms. Despite this, pulmonary impairment due to silica inhalation may proceed undiagnosed because (a) the disease usually takes several years to develop; (b) the affected individual ages during that interim and may smoke cigarettes or be exposed to significant air pollution; (c) the clinician may fail to inquire about the individuals' occupational history. It is also probable that since the lung normally has reserve capacity, significant damage could occur before it became clinically manifest.

Second, individual versus group effects must be considered. The acute loss of 200 or even 500 ml of $\text{FEV}_{1.0}$ in a male with a normal $\text{FEV}_{1.0}$ of 4.0 liters might clinically pass unnoticed. However, this same loss in a population exposed to silica would be epidemiologically significant. Since the population would contain individuals with already compromised pulmonary function, this additional loss could be critical.

Choosing the appropriate test to determine subtle effects from silica is important. While chest x-ray is the old standby, it has recently become clear that silica nodules, invisible to x-ray, can be found in workers with relatively mild exposures who have died from other causes (32). Pulmonary function tests may show effects earlier than x-ray, but this is unclear because unfortunately, it has not been common practice to measure baseline pulmonary function in workers prior to their exposure to silica.

Although it is well known that simple silicosis (diagnosed by x-ray) exists without profound clinical symptoms, it is not known how much silica (or silicosis) in the lung predisposes an individual to the development of massive fibrosis. This is an important question because progressive massive fibrosis (PMF) can occur in the absence of further silica exposure. At the present time, factors determining progression remain unclear.

Confounding

Apart from personal differences in work practices, smoking habits, etc., there are innate differences in individuals and their response to silica. This is clearly the case in Caplan's syndrome which probably occurs at a subtler level of disease and by different, little understood mechanisms. Parkes provides reference to a study of fluorspar miners in Sardinia in which

resistance and predisposition to silicosis may be genetically determined (22).

The study of health effects from silica inhalation in smokers has revealed a fairly wide variation in response. When the smoking habit is considered in workers exposed to silica, the problem is obviously compounded. The potential outcome of cigarette smoking is chronic obstructive pulmonary disease (COPD). In a cigarette smoker exposed to silica, the result is frequently mixed pulmonary disease. Given any such individual, apportioning risk to the two factors is difficult if not impossible. On a group basis, however, proper statistical techniques should be capable of allocating risk (28).

Despite the fact that silicosis has been a common, occupationally related disease for many years, only a few studies have been directed toward its epidemiologic aspects. This is probably due to the many difficulties associated with monitoring the health of a population over a period of time; the paucity of epidemiologists interested in occupational disease; and the difficulty of determining a lifetime dose of silica. On the other hand, data have existed for years that are relevant to standard setting, and "old" studies are remarkably compatible with newer "sophisticated" studies in pointing to a safe level of exposure.

Several old studies conducted by the Public Health Service revealed tragic amounts of silica exposure and silicosis in hard rock mining (12) (15). In addition, Harrington and Lanza demonstrated very high rates of silicosis in Butte copper miners (10). Later, Dreesen et al. reported silicosis with concentrations of silica dust ranging from 2 to 37 million particles per cubic foot (mppcf). No cases were seen in workers whose exposures were 10 years or less in duration with concentrations averaging 18 mppcf (5). Vitaly needed are studies that look at exposures over a working lifetime and that also consider the health of the worker after exposure stops, i.e., after retirement.

Flinn et al. studied metal miners during the period 1958 to 1961 (6). This study, involving 50 mines, included over 14,000 employees and 14,480 impinger samples. The quartz content varied from a reported 2% - 95%. Dust levels ranged from 0 to over 50 mppcf. The health assessment consisted of a medical history, occupational history, pulmonary function tests, and chest x-rays. Not surprisingly, a relationship was

found between duration of exposure and prevalence of silicosis. Workers whose exposure had not exceeded 5 years duration were unaffected. Workers who had been exposed for 30 or more years had prevalence rates exceeding 60%.

All studies of work populations exposed to silica raise the problem of previous exposures to higher levels. No exception was the study by Renes et al. involving iron foundries (24). Almost 2,000 men were examined and over 9% were found to be affected. Those who had worked for 20 or more years had a prevalence rate of 25.8%. Over 80% of the air samples were below 6.9 mppcf. But the silicosis cases were attributed to past exposures which allegedly were considerably higher.

Few studies give reliable lifetime estimates of dust exposure. An exception is the study of Flinn et al., which focused on 9 West Virginia potteries (7). Over 2,500 individuals received physical examinations and had chest x-rays taken. From this study, 189 were diagnosed as having silicosis. Impinger samples were collected to assess breathing zone exposure to silica. Quartz concentrations were measured in settled dust and ranged from 1%-39%. Table II-1 presents some of the results.

Their justifiable conclusion was that exposures should be kept below 4 mppcf if new cases were to be avoided.

The early devastation caused by silica exposure seems to have caused some people to be satisfied with improved conditions. Few rigorous attempts to prove safety have been made, and much reliance has been placed on old techniques and clinical diagnoses. An example of this is the study by Rajhans and Budlovsky in which workers in an Ontario brick plant were studied (23). While they claim no cases of silicosis have appeared in this industry, it is not clear that this group is entirely free of respiratory disease. First, they relied primarily on 70 mm chest x-rays which provide less definition than the standard 14 x 17" x-ray. Second, there were few workers who had long employment histories. Perhaps the most interesting question raised by their paper is that of the possible interaction of other dusts in the environment. Certainly the physical-chemical qualities of dusts are different. Exactly how these different qualities effect pulmonary response is not clear. A study done earlier by Keatinge and Potter revealed similar results in a British brickworks (14).

Table II-1
RELATION OF DUST CONCENTRATION AND LENGTH OF EMPLOYMENT
IN THE POTTERY INDUSTRY TO SILICOSIS*

Dust Concentration million particles/cu ft	Years in Pottery Industry				
	0-9	10-19	20-29	30-39	Over 40
0-3.9:					
Cases of silicosis	-	1	1	-	-
Workers exposed	481	223	65	21	8
Percentage	0	0.4	1.5	0	0
4-7.9:					
Cases of silicosis	1	6	26	27	29
Workers exposed	321	198	110	53	34
Percentage	0.3	3	24	51	85
8-15.9:					
Cases of silicosis	-	8	5	10	10
Workers exposed	176	119	25	17	14
Percentage	0	7	20	59	71
Over 16:					
Cases of silicosis	13	33	10	5	4
Workers exposed	363	174	21	7	5
Percentage	4	19	48	71	80

*Includes 1st, 2nd, and 3rd stage cases.

Fulton et al. came up with different results in a Pennsylvania brickworks (8). The material used to make the brick was significantly different from that in Ontario; it contained more quartz and less aluminum. Very high prevalence rates of silicosis were found in this population. Silicosis was found at all levels of exposure, except below 2 mppcf. It was also found to be more prevalent in workers involved with burned brick (which contained tridymite and cristobalite) than with "green" brick. The silica content of both was high.

While it appears the Flinn et al. study (7) considers safe levels to be below 4 mppcf and the Fulton et al. study (8) considers safe levels to be below 2 mppcf, it is important to note the proportion of silica in these dusts is different.

The granite industry in Vermont has been the source of much useful data relevant to the public health questions about silica. This industry, no different from others involving silica exposures, produced its share of disability and death. The cemetery at Barre, Vermont provides dramatic reminders of the early tragedies associated with this industry. It is said that granite

cutters, learning of their affliction with silicosis or silicotuberculosis, spent the last months of their lives producing their own gravestones.

The original study of Vermont granite workers was carried out by Russell et al. They found "universal occurrence of silicosis among the workers" and "appallingly high death rates from tuberculosis" (26). A later study by Russell et al. documented cases in occupations where the dust exposure averaged 3-9 mppcf (25). As in most studies, the question of earlier exposure to higher levels was raised. They recommended a safe limit of 9-20 mppcf for dust containing 35% silica. Russell later recommended a standard of about 10 mppcf.

It is clear that measures to control dust in Vermont had a tremendous impact. Wet methods and local exhaust ventilation established about 1937-1940 have greatly diminished the health risk.

Hosey et al. conducted an environmental study of the Vermont granite industry and demonstrated that few exposures exceeded 5 mppcf (13). The prevalence of silicosis diagnosed by x-ray decreased from 45% in 1937 to 15% in

1956. This group reported that only one new—but questionable—case of silicosis occurred in a worker beginning work after “dust control” (1940).

Ashe and Bergstrom found no new cases of silicosis in workers exposed for up to 26 years at levels of between 3-5 mppcf (1). However, they wisely suggested continued environmental and medical surveillance. This entire population was again restudied cross-sectionally by Theriault et al. (27)(28)(29) and longitudinally by Musk et al. (20).

In 1969, the Harvard School of Public Health joined with the Industrial Hygiene Division of Vermont in a comprehensive study of the relationship between exposure to granite dust, percent quartz content of the dust, and lung disease among granite shed workers exposed for many years to low levels of granite dust. To estimate current dust exposure in the granite sheds of Vermont, 784 personal respirable dust samples collected from 13 occupational groups in 49 granite sheds; 483 of these samples were analyzed for quartz content (27). A lifetime estimate of exposure to granite dust and quartz was calculated for each worker from the dust concentration data and a complete occupational history. Five indices of exposure were developed, and dust-year was selected by a multiple regression analysis as the index most highly correlated with changes in vital capacity (FVC). (Current dust and quartz concentrations in the granite sheds differ from previous estimates due to differences in sampling and analytical techniques.) Important conclusions reached from these studies are: 1) It was determined that 10 mppcf of granite dust was the rough equivalent of 0.1 mg/m³ of quartz. 2) The quartz content of the granite dust was estimated at 9%. 3) Average one year exposure was to 523 µg/m³ of granite dust and 50 µg/m³ of quartz.

The granite dust and quartz dust concentrations are presented in Tables II-2, II-3, and II-4. During the period of the study, the average granite dust concentration was 523 µg/m³; quartz averaged 50 µg/m³. Exposures were adjusted to these quantities and called a dust-year. It must be stressed that in the last decade, major changes in dust sampling and dust analysis have taken place. Personal lapel sampling has replaced fixed location sampling, thereby providing a better estimate of the dust actually breathed by the workers. Mass respirable sampling now provides mass dust concentration data rather than the

count concentration from the impinger sampling technique used earlier. Although these changes have improved the accuracy of estimating dust exposure, they have presented a challenge in establishing a lifetime dust and quartz exposure.

In calculating lifetime dust exposures, workers employed prior to 1940 were assumed to have had dust exposures 10 times higher than present levels. This factor was derived from a study of a shed without dust controls (2).

Seven hundred and ninety-two active granite shed workers from Barre, Vermont were studied to estimate the effect of granite dust inhalation on pulmonary function. Based on a complete occupational history and a comprehensive evaluation of the past and present environment, a total lifetime dust and quartz exposure for each worker was established.

Effects of granite dust on pulmonary function were reported by Theriault et al. (28). When the workers were seen for their annual chest roentgenograms (provided through a comprehensive health program instituted in 1937 by the Industrial Hygiene Division of Vermont), they were asked to participate in a study of their pulmonary function and to answer a brief questionnaire on their smoking habits. Ventilatory capacity was measured with a spirometer. The forced vital capacity (FVC) and the forced expiratory volume in one second (FEV₁) were measured. Total lung capacity (TLC) was estimated from anteroposterior and lateral chest roentgenograms and the residual volume (RV) was obtained by the subtracted difference between TLC and FVC. Workers' smoking histories were grouped as follows: those who had never smoked; ex-smokers (those who had stopped smoking for six months or more); or current smokers (those who smoked one or more cigarettes a day). The amount of smoking was quantified in cigarettes per day and in years smoked.

There were three principal results based on the evaluation of lung function. The first is related to multiple regression techniques and is shown in Table II-5. While the loss attributable to dust exposure is small, it is statistically significant and could represent a significant loss if multiplied by many years and a higher than average dustiness. It also must be remembered that this loss is the average loss for the entire population which means that some individuals would be losing less and some more.

The second major finding related lifetime

Table II-2
OCCUPATIONAL CLASSIFICATION AND
AIR SAMPLING FREQUENCY

Occupation (Classification No.)	No. of Dust Samples	No. of Quartz Samples
Cutter, letter cutter (1)	258	202
Sculptor, carver (2)	32	19
Polisher, surface machine operator (3)	104	65
Sandblast operator (4)	52	30
Carbo-saw operator, contour planer, grinder, diamond-saw operator, circular-saw operator (5)	48	38
Gang-saw operator, wire-saw operator (6)	97	44
Hydraulic splitter operator (7)	17	11
Crane operator (8)	4	2
Grouter, lumper, bedsetter (9)	10	5
Stencil cutter (10)	13	8
Boring mill operator, lathe operator, tool grinder (11)	9	4
Finisher, plug drill operator (12)	40	26
Boxer, derrickman, foreman, maintenance, general air, stone washer, torch burner (13)	100	29
Total	784	483

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Table II-3
GRANITE DUST CONCENTRATION BY OCCUPATION AND SHED*

	Occupation							
	1	2	3	4	5	—	14	
	1	634	644†	583	270	212	—	476
	2	515	398†	259	230	268†	—	293
Granite Shed	3	653	696	762	392†	368	—	478
	4	576†	679†	640	411†	438	—	502
	50	601	708	565	429	480	—	523

*All concentrations expressed as micrograms per cubic meter.

†Calculated by method described in text.

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Table II-4
QUARTZ CONCENTRATION BY OCCUPATION AND SHED*

		Occupation							
		1	2	3	4	5	—	14	
Granite Shed	1	93	95†	54	13	19	—	48	
	2	54	35†	11	12†	12†	—	18	
	3	72	104†	111	17	29	—	53	
	4	99	166†	86	58	60	—	84	
	—	—	—	—	—	—	—	—	
		50	61	99	46	35	36	—	50

*All concentrations expressed as micrograms per cubic meter.

†Calculated by method described in text.

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dust exposure to pulmonary function. By generating a prediction equation from individuals who had had no dust exposure, a percent predicted was calculated for workers with increasing dust exposure. Figure II-1 presents the results.

Table II-5

**EFFECT OF AGE, HEIGHT, SMOKING,
AND DUST ON FVC* AS ESTABLISHED
BY MULTIPLE REGRESSION ANALYSIS**

Independent variables	b ± SE	p
Age	29.9 ± 0.244	<.001
Height	54.7 ± 0.314	<.001
Years smoked	8.8 ± 0.183	<.01
Dust-years	1.6 ± 0.057	<.01

*FVC is dependent variable. Total R square = 0.532;
b represents regression coefficient; -4072.6 is constant used.

Quartz Effect on Pulmonary Function

It is clear that both total dust and quartz are correlated with adverse pulmonary function. While the midpoint 50% occurs 2.5 years later for quartz than it does for granite dust, these are small differences; we must be hesitant in attributing an additive effect to total dust. However, the fact that the effect of quartz on the lung is different from that of granite dust reinforces the suggestion that mass respirable quartz dust should have a TLC of its own.

The third important finding relates to the relative effects of cigarette smoking and dust ex-

posure. If regression equations are calculated for each dependent variable of pulmonary function, the data in Table II-6 result. Using models of restrictive and obstructive pulmonary disease, one would expect dust to produce the former and cigarettes the latter. If the table is examined, this indeed is the case. Dust causes the TLC, FVC, and FEV_{1.0} all to be decreased, consistent with restrictive disease. Cigarette smoking causes a decrease in FEV_{1.0} greater than the decrease in FVC and also causes an increase in RV and TLC. All these changes are compatible with obstructive disease.

Roentgenographic Changes

Chest roentgenograms of 784 granite shed workers were classified according to the UICC/Cincinnati classification, and their relationships to lifetime dust exposure, ventilatory function, and smoking habits of the workers were studied (29). Increase in dust exposure correlated with an increase in the profusion (number of opacities per unit area) and in the size of rounded opacities. Irregular opacities were related more to smoking than to dust. Forced vital capacity (FVC) was lower for people with abnormal roentgenograms and decreased with greater profusion. Residual volume (RV) increased with smoking but not with dust exposure. No trend was shown for total lung capacity (TLC). A dose-response curve for the effect of dust on ventilatory function and on roentgenograms showed that ventilatory capacity was affected earlier than the roentgenograms.

Table II-6

**EFFECT OF AGE, HEIGHT, SMOKING, AND GRANITE DUST ON
PULMONARY FUNCTIONS AS ESTABLISHED BY MULTIPLE REGRESSION ANALYSIS**

Pulmonary Functions	Constant	Age	Height	Years Smoked	Dust-Years	Multiple R
FVC, ml	-4,073	-30	+55	-9	-1.6	0.73
FEV _{1.0} , ml	-2,100	-27	+40	-12	-1.6	0.71
FEV/FVC%	115	-0.07	-0.15	-0.13	-0.02	0.35
RV, ml	-1,316	+33	+10	+24	None	0.57
TLC, ml	-5,212	None	+65	+16	-1.8	0.46

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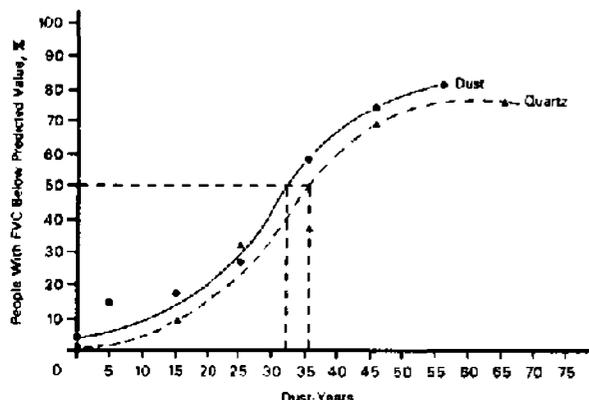


Figure II-1. Dose-response curve between granite dust and quartz and FVC.

Dose-Response for Dust on Roentgenograms

By plotting the percentage of people with opacities on their chest roentgenograms against an increasing dust exposure, one derives a dose-response which gives an estimate of the toxicity of the dust (Figure II-2). On the y axis are the percentages of people with radiographic opacities, and on the x axis is the increasing exposure expressed in dust-years. One dust-year is defined as an exposure for one year to the average dust concentration in the granite sheds—523 $\mu\text{g}/\text{cm}$ of granite dust. The curve shows a plateau at around 30% of workers with exposure from 0-35 years. After that, the curve increases dramatically; at an exposure of 55 dust-years, 60% of the granite shed workers have opacities. The point at which 50% of the active workers are affected may be the best estimate of the toxicity of the dust and could serve as a means of comparison with other toxic materials. In this study the 50% dose-response is estimated at 46 dust-years of exposure.

Dose-Response for Roentgenograms and Ventilatory Function

In Figure II-3, we have plotted the proportion of people with abnormal roentgenograms against the dust exposure. The curve obtained from a similar study establishing dust effect on pulmonary function has been superimposed (28). The comparison is weakened by the fact that the curve starts at 30% for roentgenograms; nonetheless, by comparing the midpoint 50% of the two curves, it allows us to compare the effects.

While it takes 32.5 dust-years of exposure to affect the ventilatory function of 50% of the workers, it takes 46 dust-years to produce opacities on 50% of the worker's radiographs. There is a delay of about 13.5 years between the appearance of signs of dust effect on pulmonary functions and on roentgenograms. It can be argued that early detection of the effects of dust in *groups* of workers is better accomplished by pulmonary function tests than roentgenograms.

Morgan has criticized these results because only one reader read the x-ray films and because there was a high rate ($\sim 30\%$) of radiographic abnormalities at zero dust readings (17). Both criticisms are valid, but it should be pointed out that had the x-rays not been "over-read," the discrepancy between pulmonary function and x-ray results would have been even greater.

Morgan also minimized with some justification, the significance of 2 ml loss of ventilatory capacity for each dust-year of exposure (17). It is important to note, however, that cross-sectional studies have certain inherent weaknesses. Usually the population is a "survivor" population in that persons who contract serious pulmonary disease leave because they cannot work.

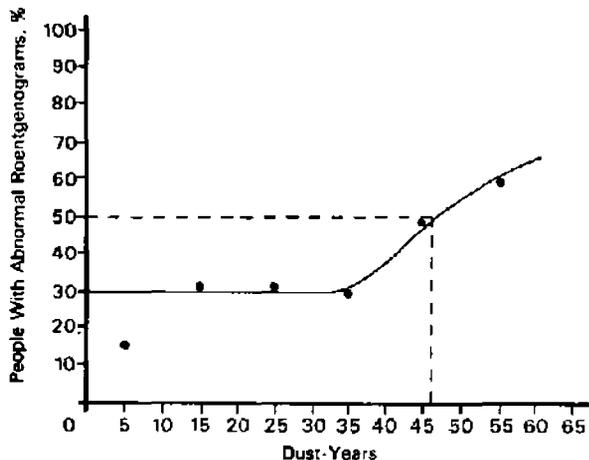


Figure 11-2. Dose-response curve of granite dust on roentgenograms.

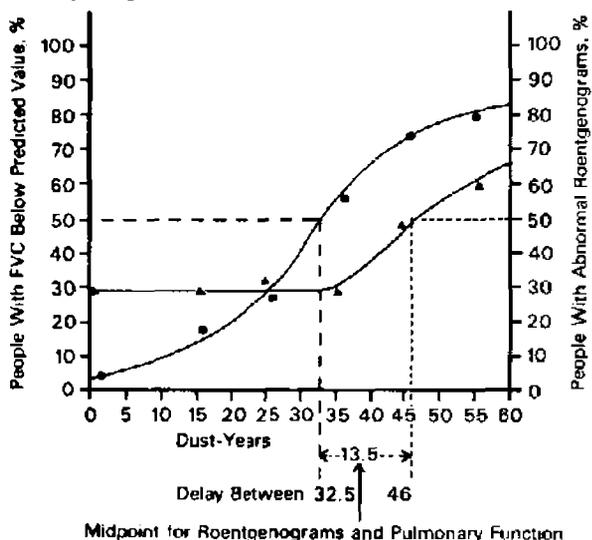


Figure 11-3. Dose-response curve of dust on roentgenograms (triangles) and FVC (circles).

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Also, since many of the independent variables of interest (age, years of smoking, years on job, dust-years) are inextricably correlated, statistical tests have difficulty in giving valid attribution to each.

These problems argue for the use of prospective studies which, among other advantages, provide the opportunity to assess the impact of dropouts from populations. The prospective model measures change in lung function over time and correlates the magnitude of change with the level of exposure. Instead of estimating changes from cross-sectional data, real changes are measured. Such a study was conducted by Musk et al. on the same Vermont granite workers (20). Pulmonary function studies were performed on 974

workers in Vermont granite sheds in 1974. Of these subjects, 668 had been studied 4 years earlier and had remained in jobs in which their exposure to granite dust was assumed not to have changed, based on dust concentrations measured during 1970. The yearly decrement in pulmonary function observed in the 668 granite shed workers was excessive (0.07 to 0.08 l/yr for FVC and 0.05 to 0.07 l/yr for FEV₁). This exceeded the expected decrement derived from several other occupational and population groups. Published cross-sectional and longitudinal data usually indicate a decrement of no more than 0.03 l/yr. in both FVC and FEV₁ (20). The observed decrements were independent of exposure groups and not accounted for by cigarette smoking. In 528 additional granite shed workers, decrements in ventilatory capacity had been measured for 1, 2, or 3 years and were consistently of the same order of magnitude. Dust concentrations within defined jobs and between granite sheds showed great variability. Despite this, a suggestive relationship between exposure and decrement in ventilatory function was demonstrated at the end of 2 years; however, at the end of 4 years, the relationship could no longer be shown with these exposure groupings. The difficulty in characterizing individual dust exposures and projecting dust concentrations for several years is considered to account for the absence of a dose-response relationship at the 4 year follow-up. The most important result of this study is evidence that previous estimates of lung volume loss among granite shed workers (2 ml/dust-year loss in lung capacity) were underestimates. It was concluded that present dust concentrations in Vermont granite sheds cause excessive deterioration of lung capacity.

A recently published article (9) challenged the findings of Musk et al. (20). This study concluded that technical deficiencies in the Musk study "led to exaggerated and erroneous estimates of loss." They correctly pointed out that the FVC's taken between 1970-1974 did not meet current ATS criteria. The "Harvard group" is currently reanalyzing their tracings and applying ATS criteria to determine how much, if any, their conclusions will be changed.

Discounting the "Harvard group" studies involving pulmonary function still leaves several studies, old and new, that suggest exposure to silica at levels below 100 $\mu\text{g}/\text{m}^3$ causes x-ray (7)(8)(21)(25)(29) and pathological changes (32).

Morgan presents a case for (what he calls)

industrial bronchitis; he considers it relatively harmless (18). Morgan suggests the observed losses could be a "non-specific response to dust alone" (17). This is certainly possible, but some recent evidence raises doubt about this being the complete explanation.

Vallyathan and Craighead examined the lung sections of 19 deceased Vermont granite workers (32). Examinations were accomplished with light and polarized light microscopy, scanning and backscattered electron microscopy, x-ray energy and x-ray fluorescent spectrometry, and x-ray crystallography. Medical histories, chest x-rays, and pulmonary function tests were available for all 19 individuals. Fifteen of the 19 had begun work after dust control (1937). All of the workers had *clinically normal* x-rays and pulmonary function tests, but dust-related fibrotic lesions were present in all lungs. None had confluent of severe fibrosis, but all had varying degrees of focal fibrosis. The quantity of silicon in each lesion was approximately the same as that found in lesions of persons with clinical silicosis. The authors concluded fibrosis can clearly begin before being detectable by standard clinical approaches (chest roentgenograms and pulmonary function tests).

All of the studies described in this section provide evidence for adverse pulmonary effects at levels of exposure above 10 mppcf or 0.1 mg/m³. Some showed that foundry workers exposed to the equivalent of 0.05 mg/m³ of quartz developed silicosis while those with less exposure did not (21). All the Vermont findings were seen with an average exposure around 0.05 mg/m³ of quartz. It is possible, however, that since this was the average exposure, individuals whose exposure exceeded this level accounted for the noted effects. [The "no effect" level was probably below 0.05 mg/m³, but available data did not allow accurate determinations.]

ESTIMATE OF POPULATION AT RISK

In the United States, occupational exposure to silica occurs in several large categories of industry; in particular, mining, manufacturing, construction, and agriculture. The U.S. Bureau of Census Statistical Abstracts for 1971 provides the statistics in Table II-7.

A recent NIOSH estimate reveals that a more accurate number for metal mining is 300,000 instead of 76,000 (16). This Table also leaves out

2.5 million agricultural workers; 0.6 million workers in the chemical and allied products industry; and 0.6 million workers in heavy construction who may be at risk. There are many other miscellaneous industries in which silica exposure may take place.

The current state of our knowledge does not permit accurate estimates of the incidence and prevalence of silicosis. Systematic studies of all the above industries would need to be conducted. If either extensive information on silica exposures or health effects were available, the magnitude of the problem could be estimated. This lack of information is not unique to the silica problem. Attempts to estimate the prevalence of all of the occupational diseases results in similar frustration.

Table II-7

EMPLOYMENT IN INDUSTRIES HAVING POTENTIAL EXPOSURE TO FREE SILICA 1970

Metal mining	76,000
Coal mining	125,000
Nonmetallic minerals (except fuels)	95,000
Stone, clay, and glass products	507,000
Iron and steel foundries	188,000
Nonferrous foundries	69,000
Cement production	3,212,836
Total	4,272,836

PATHOLOGY

It is beyond the scope of this chapter to review the details contained in many sources. The interested reader is referred to Parkes (22), Morgan and Seaton (19), and books on the pathology of the lung.

Findings on Gross Examination

Fibrous adhesions are commonly found in the pleural cavity with plaques visible over the pleural surface. The hilar nodes are frequently enlarged and sometimes calcified. The lung may be hyperpigmented. On cut sections, the lung reveals grayish nodules, usually in the superior-posterior aspects of the respective lobes. These can range in size from small to large (3 mm to 1 cm) and can also vary in profusion. Nodules in both the lung parenchyma and in the lymph

nodes show a whorled appearance (Figure II-4). In severe cases, nodules may coalesce and be associated with tuberculous infection or necrosis and cavitation (Figure II-5). Associated with this coalescence is prominent contraction of the upper lobe(s)—a striking radiographic feature of the advanced disease. Evidence of congestive heart failure may exist with corresponding enlargement of the right side of the heart.

Microscopic Findings

The classical silicotic nodule is usually located in the area of the respiratory bronchiole. The nodule is composed of reticulin fibers in the periphery and collagen fibers in the center. Fibroblastic activity is usually evident around the periphery of the concentric lesion (Figure II-6).

The airways and blood vessels are frequently destroyed by being entrapped in the fibrotic nodule. Silica particles are difficult to identify in tissue sections by polarized light microscopy. Therefore, special techniques involving high resolution microscopy are required. It appears that the extent of the lesion bears little association with the amount of silica present.

In cases of massive fibrosis the normal pulmonary structure may be distorted or destroyed. When there is coexistent mycobacterial infection, the characteristic histological feature of tuberculosis may not be observed. It is, therefore, important to stain and/or culture the lesion for acid fast bacilli in all cases showing massive fibrosis.

Acute Silicosis

Since this disease develops so rapidly, the pathologic picture is very different from the chronic form. Please see the Acute Silicosis monograph, page 239.

Pathogenesis

Much experimental work has been done to elucidate the mechanism of silica's action. The work of Heppleston has been particularly noteworthy in revealing several important steps (11):

1. Destruction of macrophages by the ingested silica particles.
2. The production of more macrophages to continue ingesting silica particles.
3. Stimulation of collagen formation.
4. Hyalinization of the collagen.

After lung macrophages have been damaged, additional macrophages appear to engulf

liberated silica particles and they die too. Then a reticulin network is formed. Finally, the collagen is laid down and is hyalinized. There is evidence that silica somehow stimulates lipid factors which in turn promote the production of more macrophages. A nonlipid material is also produced by macrophage death; this material stimulates fibroblasts to produce collagen. The hyalinization step may be related to immunoglobulins.

While the information described above has been derived primarily from animal studies or studies of cell cultures, the implications for man are fascinating. For example, we currently measure silica exposure primarily as a mass measurement, partially ignoring the distribution of particle size. Depending on particle size, there can be many more or fewer particles for the same mass. Does the macrophage recognize a particle's size? Is the number present more impor-

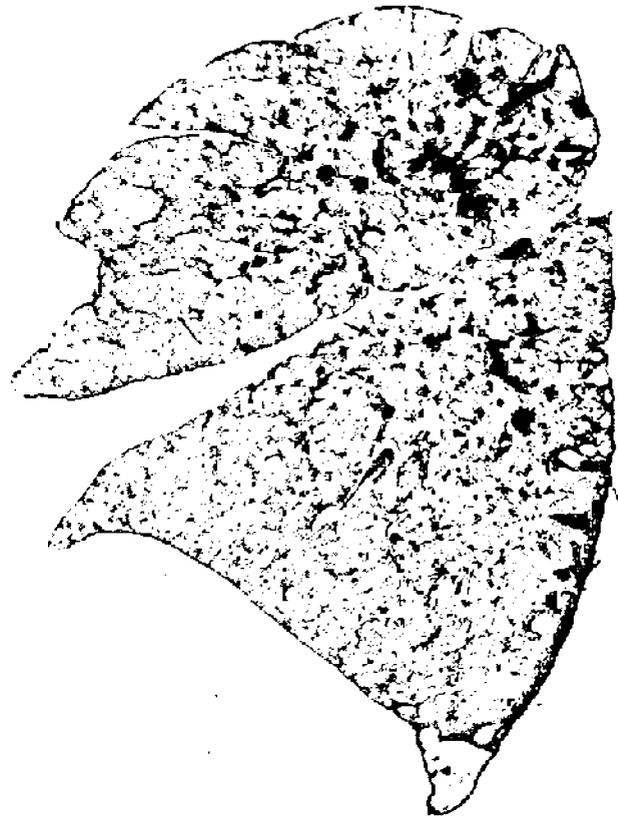


Figure II-4. *Simple Silicosis*—The whole lung section shows numerous discrete rounded nodules, typical of simple silicosis. The nodules are more numerous in the upper lobes and have pale centers with darkly pigmented outer borders.



Figure II-5. Conglomerate Silicosis (progressive massive fibrosis PMF)—The whole lung section shows a large central area of fibrosis composed of multiple coalescent rounded nodules with pale centers typical of conglomerate silicosis. The patient was a coal miner and the lung also shows the macular lesions of coal workers' pneumoconiosis.

tant? Macrophages engulf silica particles of respirable size; could there be differential treatment based on particle size? We know the same silica mass might be associated with differing numbers of particles because of different size and potentially have an effect on varying the number of macrophages. The answers are important so as to know the most meaningful way of assessing exposure for humans facing the risk. Although differences in gravimetric and impinger sampling are known to be poorly correlated, differences in particle size and surface properties are clearly important in terms of biological effects.

It is not fully understood why some individuals develop massive fibrosis while others do not. Several factors may be important. The dose of silica is, of course, important and relates to both the induction period as well as the

severity of disease. Cigarette smoking is also an important factor and will be considered later. Immunological status is another important factor. Persons with rheumatoid arthritis react differently to silica exposure both in quality and quantity. Other immunological host factors are probably important too. Concurrent infection is likewise important. The relationship to mycobacterial infection has been known for years. Other microbiological infections are likely to be important as well.

Acute silicosis is primarily related to massive silica exposure. The general pathological findings that have been described differ from chronic silicosis. This may relate to the usual pulmonary defense mechanisms being overwhelmed.

CLINICAL DESCRIPTION

Symptoms

Dry cough may be an early manifestation of silicosis. As the disease advances, the cough may become more prolonged and distressing and be associated with sputum production. Hemoptysis is not common. Breathlessness is a common symptom as the disease progresses. Initially, shortness of breath occurs during heavy exercise; less and less exercise is required to induce dyspnea as the disease progresses. Wheezing is not common unless the disease is accompanied by asthma, or if there is significant large airway distortion (such as the distortion occasionally seen in PMF). There is a variable association between shortness of breath and either pulmonary function results or opacities seen on chest x-ray. Usually general health is not impaired in simple silicosis. Pneumothorax is common in advanced stages and respiratory failure is an important consequence of progressive massive fibrosis (PMF). If silicosis is associated with tuberculosis or congestive heart failure, general health obviously deteriorates. In advanced silicosis, respiratory failure precedes cor pulmonale and ultimately, congestive heart failure.

Physical Signs

In late stages, physical findings similar to those found in other chronic fibrotic and obstructive lung diseases occur. Bronchitic symptoms and signs are common. Hypoxemia is usually present in advanced cases even without cyanosis or congestive heart failure. The ability to expand the chest is not impaired until late in



Figure II-6. Silicotic Nodules—Three silicotic nodules in a coal worker's lung. Note concentric arrangement of collagen fibers. Pigmented macrophages are present in the silicotic center and in stellate mantle surrounding the lesion. The paucity of pigment in the remainder of lesion is characteristic. Hematoxylin and Eosin \times 200.

the disease. For the most part, percussion is not affected until late in the disease, and this is usually related to pleural fibrosis. Unless the disease is complicated by chronic obstructive pulmonary disease or tuberculosis, adventitious sounds are not commonly heard on auscultation. In the late stages of silicosis, signs of right ventricular hypertrophy and eventually right heart failure will appear, generating cor pulmonale and ultimately congestive heart failure.

Lung Function

Until the disease is fairly far advanced, effects on pulmonary function are minimal to moderate. There may be some slight reduction in vital capacity and some depression of arterial oxygen tension (hypoxia), particularly on exercise. It is difficult to characterize individual cases, however, as one rarely has baseline pulmonary function values available for comparing the current state of an individual.

The correlation of pulmonary function tests with radiographic classification is weak on a clinical basis, unless progressive massive fibrosis is present. The disease is manifested by a restrictive pulmonary pattern on pulmonary function tests. For example, TLC, VC, and RV are all likely to be decreased. In the absence of massive

fibrosis, oxygen desaturation is rare at rest or during mild exercise but may be observed on greater effort in some individuals. Although defects in diffusing capacity are not common, as the disease progresses there may be some effect on gas transfer.

Radiographic Appearance

The most common x-ray evidence of silicosis is the appearance of small discrete round opacities, which usually occur in the upper halves of the lung fields and vary in size from approximately 1 - 3 mm in diameter (Figure II-7). As the disease progresses, the opacities increase in size and number and begin to affect the lower parts of the lung as well as the upper lung fields. Nodular coalescence, upper lobe contraction, hilar retraction toward the apex, and basilar emphysema form an important diagnostic radiographic pattern in complicated silicosis (Figure II-8). With further progression of the disease, larger opacities are seen which could be described as conglomerate masses. In some severe cases these opacities can occupy the greater part of the lung field on a radiograph. The progression is variable in speed and obviously relates to dust exposure and host factors. Sudden progression or sudden worsening of the x-ray picture often



Figure 11-7. Simple Silicosis—Posteroanterior radiograph showing multiple discrete rounded nodules (1-3 mm in diameter) primarily in the upper mid-zones.

heralds the onset of a superimposed mycobacterial or fungal infection. In some cases, the sudden worsening of the disease may be associated with the rheumatoid factor being present. This is referred to as Caplan's syndrome and may be associated as well with the onset of rheumatoid arthritis (3). Calcification can sometimes complicate the picture on x-ray. This calcification can not only affect the silicotic nodule itself, but can also affect the fibrous lymph nodes. Frequently, lymph node calcification is characterized by a very thin, dense ring of calcification known as eggshell calcification. Pleural fibrosis, while uncommon in early stages of silicosis, may occur—particularly in advanced cases.

Other Tests

Ordinarily, if other clinical tools are available, acquisition of pulmonary tissue is not necessary to make the diagnosis of silicosis. In the face of rapidly advancing silicosis, it is important to acquire sputum samples for culture and to rule out mycobacterial and fungal infections.

Tests for rheumatoid and antinuclear factors should be performed. Electrocardiography may be useful in advanced cases to establish or refute the presence of right sided heart failure.

Clinical Complication

From the previous discussion, one should also think of the possibility of superimposed mycobacterial infection. In advanced cases, the possibility of cor pulmonale exists. Bronchitis is a frequent accompaniment of silicosis and may be the result of concurrent cigarette smoking. It is not certain whether silica itself causes bronchitis. Emphysema is sometimes seen in lungs of silicotics; it may be more related to cigarette smoking than to dust exposure, although the basilar emphysema characteristic of advanced silicosis is probably specifically related to the upper lobe contracting from massive fibrosis. The rapid progression of silicosis in the presence of rheumatoid arthritis or the rheumatoid factor has already been mentioned and should be kept in mind. Bronchial carcinoma is sometimes seen in individuals with silicotic lungs, but with our



Figure 11-8. Progressive Massive Fibrosis (PMF)—Posteroanterior radiograph showing a significant loss of lung parenchyma. Basilar bullae, bilateral upper lobe conglomerate lesions, with compensatory emphysema and elevated hila are seen.

present knowledge, there is little evidence to suggest it occurs more frequently in silicotics than in nonsilicotics (33). In a miner with lung cancer, the possibility of exposure to radon daughter products should be entertained.

Treatment

There is no specific treatment for silicosis. Corticosteroids do not appear to affect the progression of the disease. Detecting and treating concurrent tuberculosis is essential. In addition, appropriate treatment for congestive heart failure should be begun if this complication exists.

DIAGNOSTIC CRITERIA

In the presence of an adequate occupational history revealing work exposure to silica, the diagnosis of simple silicosis is usually straightforward. Roentgenographic changes are relied on by most clinicians for the diagnosis. While the

argument is frequently made that changes on chest x-rays precede other clinical findings, there is now some reason to doubt that. Mild restrictive disease detected by pulmonary function may occur in workers with early x-ray manifestations. It must be remembered by the clinician that an FVC of $\geq 80\%$ predicted is considered normal. On the other hand, if there are 100 men who have early x-ray evidence of silicosis whose average FVC is 90% of predicted, this comprises an abnormal population. Clinicians are usually at a disadvantage seeing individuals one at a time, and they frequently have no baseline chest x-ray or pulmonary function test results for comparing current clinical findings.

Given an individual with exposure to silica, a mild restrictive defect would suggest early silicosis; likewise small round opacities on the chest x-ray would support the diagnosis. With minimal loss of pulmonary function or minimal

chest x-ray abnormality, symptoms such as shortness of breath are unlikely to be a clinical feature unless associated with underlying chronic airways disease.

When it comes to complicated silicosis, PMF, or Caplan's syndrome, the diagnosis is more difficult. The possibility of a lung tumor or tuberculosis must be considered. Bacteriological testing of sputum usually reveals mycobacterium tuberculosis. A lung biopsy may be necessary to diagnose carcinoma.

Abnormalities of diffusing capacity are not common or profound in early silicosis. Similarly, clubbing and physical signs in the chest, while not ruling out silicosis, suggest other diseases. Hyperinflation, reduced breath sounds, prolonged expiratory phase, and reduced expansion of the chest are among the most common physical findings in advanced silicosis.

Acute silicosis should be suspected in a worker with massive exposure to silica, e.g., an unprotected sandblaster. Mycobacterial infection occurs in about one-quarter of these cases. Symptoms of progressive shortness of breath are common. Weakness, weight loss, diffuse rales, and even cyanosis can be seen. Usually there is evidence of massive disease on chest x-ray, with the diaphragm frequently being high. Pulmonary function is severely compromised.

PREVENTION

The theoretical approach to preventing silicosis is simple: reduce airborne dust concentrations to safe levels. This implies cognizance of safe levels and feasible utilization of technical means to control dust exposures. While there remain some questions about the safe level, technology is available to achieve at least the 50 $\mu\text{g}/\text{m}^3$ level in most situations. The ACGIH *Industrial Ventilation Manual* provides ventilation designs appropriate for foundries, ceramics industries, crushing, grinding, and screening operations. Since sandblasting generates so much dust and is so difficult to control, and since other substitute techniques are available, this practice should be prohibited.

Other existing techniques such as enclosure, isolation, local exhaust or dilution ventilation, and wet processes are highly effective methods of controlling dust exposure. As a last resort, in unusual and temporary situations, protective respirators can be employed effectively.

Since perfect knowledge does not exist as

to safe levels of exposure, medical surveillance techniques should be continued, not as control methods, but to verify the adequacy of the standard and the meeting of the standard. Both pulmonary function tests and chest x-rays should be employed at appropriate intervals. [NIOSH recommends chest x-rays and pulmonary function studies be utilized prior to employment placement and at least once each 3 years thereafter. (Criteria for Recommended Exposure to Crystalline Silica, NIOSH Publication No. 75-120)]

RESEARCH NEEDS

Research should be directed toward the elimination of silicosis. In addition, questions concerning the subclinical effects of silica exposure must be answered, e.g., at what level of exposure do fibrotic lesions appear in the lung? If exposure at that point is stopped, do the lesions remain static or do they progress?

Aside from the questions concerning health effects, questions about environmental assessment are important. For example, does mass respirable sampling provide a better or worse way to assess biologically meaningful exposure? Are there ways to measure and compile worker exposure to silica so that accurate lifetime exposure can be assessed? Is the effect of silica modified (antagonized or enhanced) by concomitant exposure to other dust?

The role of animal, tissue, and cell studies must also be considered. Are there nonhuman tests that allow accurate prediction of human toxicity? Are there ways of simulating 40-year human exposures in animals?

Engineering approaches to problem solution need to be considered. Are there better ways to process these materials so as to minimize dust exposure? Are better engineering techniques available to control existing processes?

Policy issues likewise need research. What are the best ways to create a climate that facilitates both occupational health and productivity? Are there economic incentives that would promote this? Is regulation and enforcement the best method?

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ACUTE SILICOSIS

Daniel E. Banks

Acute Silicosis, or silico-proteinosis, is a rare presentation of silica-induced lung disease (Table II-8) (10). This form of silicosis is associated with massive exposures to respirable size particles of high free crystalline silica content over a short period of time. Invariably, this disease is untreatable with a lethal outcome. Betts, in 1900, first described this acute presentation of silicosis in the United States and his description is relevant today (4):

After coughing has continued for some time there will be . . . loss of appetite, loss of weight and shortness of breath, the respirations running as high as 38 to 42 breaths per minute on the slightest exertion. As the weeks pass, the patient suffers general malaise and soon finds it impossible to get about. . . in (the disease's) later stages, the temperature may rise to 102 or 104. . .

Early reports related acute silicosis to miliary tuberculosis because of the similar rapid downhill course (11). Other early reports described similar presentations in workers who mixed silica and alkali in the production of industrial abrasives (7)(9). Postmortem examination of the lung in these cases revealed (6):

The presence in every alveolus of large amounts of pink staining fluid, (and) an extreme grade of edema with a very high protein content. Another interesting finding is the presence of epithelium in all the alveoli.

The pathologic and radiographic features of acute silicosis were fully described in 1969. Buechner and Ansari described 4 sandblasters with a mean silica dust exposure of only 4 years, and relentlessly progressive dyspnea, cough, fatigue, weight loss, and pleuritic chest pain (5). Despite the prompt diagnosis and treatment of tuberculosis in 3 cases and appropriate therapy of suspected tuberculosis in the 4th, mean survival time from onset of symptoms was only 7.5 months. All died from respiratory failure.

In all, chest radiographs showed air bronchograms and an alveolar filling pattern. Each man had significant restriction of lung volumes.

Pathologically, the alveolar septae were thickened and infiltrated with mononuclear cells. The lungs were firm and heavy with a pinkish, proteinaceous PAS positive staining alveolar exudate (Figure II-9) identical to that seen in idiopathic alveolar proteinosis and has resulted in the use of the term silico-proteinosis. Typical silicotic nodules were seen in 2 cases, but these were smaller than nodules noted in the chronic form of silicosis.

More recently, Suratt et al reported acute silicosis in 4 tombstone sandblasters (12). These cases were similar to those above in both mean duration of exposure (4 years) and mean survival from onset of symptoms (6 months). Two had pneumothoraxes complicating their clinical course. One developed focal glomerulonephritis and another systemic lupus erythematosus (both had positive anti-nuclear antibodies, a common finding in sandblasters' silicosis (8)). All 4 had a restrictive impairment on spirometry with a significant decrease in diffusing capacity. No chest radiographs revealed the pattern of silico-proteinosis described above. Instead, 2 showed bilateral upper lobe opacities, and 2 showed a reticulonodular pattern.

Despite the absence of a radiograph appearance of silico-proteinosis, postmortem lung examinations in two sandblasters revealed a PAS positive exudate filling the alveoli. Discrete hyalinized and cellular nodules were present in alveolar walls and within the wall of small pulmonary blood vessels. The authors considered these pathologic changes as intermediate between silico-proteinosis and chronic nodular silicosis.

Evidently, then, there is variability in chest radiographs of workers with massive silica dust exposures over a short period. Classically, alveolar infiltrates with air bronchograms are present and correlate with PAS positive proteinaceous

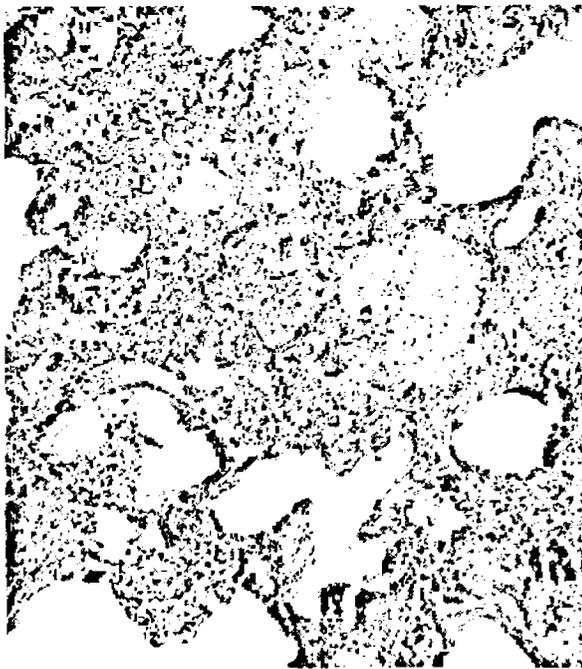


Figure II-9. Photomicrograph (Hematoxylin & Eosin, 50X) from a lung biopsy specimen of a surface coal miner driller who died 26 months after the diagnosis of acute silicosis was made. The photomicrograph shows distorted pulmonary parenchyma, interstitial inflammation and fibrosis and filling of the alveolar spaces with a relatively acellular material with some epithelial cells present. This material gave a positive reaction when stained with Periodic acid-Schiff reagent. (3)



Figure II-10. Chest roentgenogram of a silica flour worker showing diffuse small opacities with a lower lobe predominance, a large opacity in the right mid-lung field, and a right sided air-bronchogram.

alveolar exudate. Alternatively, simple nodular silicosis, which rapidly progresses to progressive massive fibrosis, may be present in those with short-term massive exposures.

Silicotics are particularly prone to mycobacterial infections. Bailey et al found 22 of 83 silicotic sandblasters in New Orleans developed complicating mycobacterial infections, both with typical and atypical (*M. kansasii* and *M. intracellulare*) organisms (1). All 18 (diagnosed ante-mortem) converted positive sputum to negative status under treatment. Control of tuberculosis did not prevent progressive respiratory impairment and 4 of these patients died of respiratory failure. Of the total of 8 deaths in the entire group, 3 occurred in sandblasters with silico-proteinosis.

Recently NIOSH representatives evaluated the health of miners and mill workers at 2 silica flour mills in Southern Illinois (2). Of 61 workers and ex-workers with 1 or more years of exposure to silica, 16 (26%) developed simple silicosis and 7 (11%) had conglomerate silicosis. Four of these 7 had 6 or less years of silica dust exposure. One workman developed the radiographic picture of silico-proteinosis (associated with a mid-lung conglomerate lesion) after only 2-½ years of dust exposure (Figure II-10).

As we enter the decade of the 1980's, it is vexing to acknowledge that silicosis—perhaps the oldest occupationally related disease—exists despite sophisticated control technology. Sandblasters and silica flour mill workers are 2 groups still at high risk of developing acute silicosis. Adequate compliance with current standards and continued surveillance of workers exposed to free silica is essential to prevent severe health effects.

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Table II-8

IMPORTANT CHARACTERISTICS OF THE DIFFERENT CLINICAL FORMS OF SILICOSIS (8)

Clinical Type	Pathology	Exposure Levels	% Silica in Dust	Usual Exposure Duration	Time from 1st Exposure to Disease Development (X-ray Findings)
Chronic ("Classical") Silicosis	Fibrotic nodules located near respiratory bronchioles	"moderate"	<30%	20-40 yrs.	20 yrs.
Accelerated Silicosis	Fibrotic nodules smaller than those in "classical" silicosis PMF in mid-zones	"moderate-high"	47-84%	5-15 yrs.	4-8 yrs.
"Silico-proteinosis" Acute Silicosis	Diffuse interstitial fibrosis and alveolar lipo-proteinosis	"heavy"	90-100%	3-6 yrs.	1-3 yrs.

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SILICATE PNEUMOCONIOSIS

John F. Gamble

INTRODUCTION

Silicates comprise about 25% of known minerals, nearly 40% of the common minerals, and well over 90% of the earth's crust. If the constituents of the earth's crust are pictured in terms of space they occupy, the crust is a "box-work of oxygen ions bound together by the small, highly charged silicon and aluminum ions. The interstices of this more or less continuous oxygen-silicon-aluminum network are occupied by ions of magnesium, iron, calcium, sodium, and potassium" (5). Silicates are the most important mineral class, largely constituting the soil from which we get our food. The construction material in our buildings (brick, stone, concrete, glass) are silicates or largely derived from silicates.

Silicate minerals have a crystal structure containing the SiO_4 tetrahedron arranged as isolated units, as single or double chains, as sheets, and as three-dimensional networks. Because of the diversity of these minerals, and no recognized disease entity attributable to silicate minerals, we have organized this chapter around the following mineralogical classification scheme:

Island Structures: olivine, kyanites

Isolated Group Structures: beryl, cordierite, tourmaline

Chain Structures: spodumene, wollastonite, amphiboles

Sheet Structures: kaolin, serpentines, talc, bentonite, fuller's earth, sepiolite, mica, sericite, vermiculite

Framework Structures: silica minerals, feldspar, nepheline, zeolites

Rocks in the earth's crust exhibit wide variation in chemical and mineral composition. Most occupational exposures to silicates will not be to a pure silicate but to a mixture of silicates.

A discussion of individual silicates follows.

Two silicates of common occurrence and high toxicity will be discussed separately in this section. These are asbestos (serpentine and amphibole) and silicon dioxide or quartz. Talc, containing significant concentrations of free silica and/or asbestos, will not be discussed in this chapter on silicates, as the effect on health is that of silicon dioxide and asbestos. In reported studies where an association of some health effect with exposure to some silicate is observed, the difficulty of precisely defining the concentration and assemblage of minerals must be considered. Often the probable causative agent is silica, and other silicate minerals may have little or no noticeable toxic effect. In some cases the other silicate may, in fact, be diluting or modifying the effect of silica.

Asbestos is a category of natural silicate minerals existing in fibrous form and associated with known disease patterns. There are also fibrous "rock forming silicates," variously described as acicular, asbestiform, elongate, fibrous, bladed, lamellar, filliform, prismatic, and columnar. If the 1975 OSHA standard for asbestos (length $\geq 5 \mu$; maximum diameter $\geq 5 \mu$; length/diameter ratio ≥ 3) is applied, the crushing and milling of any rock usually produces "asbestos" fibers, and many of the silicates discussed in this section would contain "asbestos" in significant quantities.

At present, there is no concurrence on the effects of silicate mineral particles on humans by minerals not generally regarded as asbestos. Nicholson, Langer, and Selikoff summarize the situation as follows (3): "The varietal nature of asbestos, its broad range of mineralogical properties, suggests that other nonasbestos silicate fibers may be active as well. The argument centering on crystal face and cleavage plane difference extrapolated to biological potential requires study. The fact that a mineral fiber is non-

asbestos does not extrapolate to its being non-active biologically."

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ISLAND STRUCTURES (SiO₄)⁴⁻

Olivine Group (Mg,F₂)₂ SiO₄

Definition

No disease or pneumoconioses from olivine mineral has been observed in humans. Animal studies reveal a foreign body type reaction and fibrosis when asbestos is present.

List of Causative Agents

Definite: --

Probable: Serpentine

Possible: Olivine

List of Occupations and Industries Involved

The olivine group of igneous rocks are iron and magnesium silicates with a low proportion of silica. They form a complete series ranging from forsterite to fayalite. The olivines vary in amounts from accessory to main constituent and are often associated with pyroxene, calcic plagioclase, magnetite, corundum, chromite, and serpentine.

Olivine is used principally in foundries, primarily as a special sand for mold-making in brass, aluminum, and magnesium foundries. It is used as a refractory material (bricks), in mixes for furnace linings, and as a source of mag-

nesium in fertilizer. There is interest in using olivine as a source of magnesium compounds and metallic magnesium.

Epidemiology—No studies.

Estimate of Population at Risk and Prevalence of Disease

The United States (Washington and North Carolina) produces only about 60,000 tons per year, but in Europe, larger quantities of olivine are used in foundry sand applications as a silica sand replacement, partly to avoid the risk of silicosis. Overall, the mining population is small and prevalence is unknown, but the lack of any reports of disease in humans together with olivine's low toxicity suggests prevalence is low.

Pathology

No reports in humans. Tracheal injection of olivine in rats reveals a foreign body type reaction with phagocytic cells congregating in the alveoli and lymphatics of the alveolar wall, with subsequent alveolar wall thickening, and with slight increase in reticulin fibers in lymph nodes.

Tracheal injection of phoscorite (which contains olivine and serpentine as major minerals and quartz and magnetite as minor constituents) produced no or grade 1 fibrosis in rats. Grade 1 fibrosis was defined as cellular lesions with some loose reticulin but no collagen.

Clinical Description—No reports.

Diagnostic Criteria

If quartz or asbestos are present, the diagnosis is that of silicosis or asbestosis.

Methods of Prevention

Keep exposures low. Olivine is less toxic than quartz and serpentine, which are both possible contaminants.

Research Needs

There are no epidemiologic studies of miners. At present the population at risk is small, and toxicity appears low. If olivine gains greater use as a silica substitute and source of magnesium, such a study should be undertaken.

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Alumino-Silicate Group (Aluminum Silicate)

Definition

This group of three kyanite minerals (kyanite, andalusite, sillimanite) occurs as accessory minerals in gneiss (hornblende) and mica schist. Mild fibrosis or pneumoconiosis may result from exposure to kyanite. Silicosis is possible if cristobalite is present.

List of Causative Agents

Definite: ---

Probable: Cristobalite, mullite

Possible: Kyanite, andalusite, sillimanite

List of Occupations and Industries Involved

Kyanite is often associated with garnet, staurolite, corundum, pyrite, layulite, rutile, mica, biotite, and feldspar. Since 1920 this group of three minerals has been in great demand for making high-grade refractories, such as in spark plugs, laboratory ware, thermocouple tubing, and refractory bricks in electric and forging furnaces and cement kilns. The process for making the ceramic ware involves calcining the raw minerals at 1500° for 24 hours, producing mullite, cristobalite, and glass. The absolute consumption of kyanite minerals will probably remain at its present level.

The largest use of kyanite is in the manufacture of refractory mortars, cements, castables, and plastic ramming mixes where it constitutes 10% to 40% of the mixture. Other uses include the manufacture of silicon-aluminum master alloys, in floor and wall tile, kiln furniture, blown aluminum silicate high-temperature insulation, brake linings, foundry mold facings, glass batch addition for alumina content, spinnable mullite fibers, ceramic honeycomb, mortars, grinding media, extrusion dies, welding rod coatings, and spark plugs.

Andalusite is less common, but deposits in California are mined for use in the manufacture of spark plugs and other highly refractory porcelains.

Sillimanite is also uncommon although large deposits are being developed in Assam, India.

Epidemiology

Examination of 13 out of 15 workers employed in a refractory and exposed to sillimanite revealed some increase in the extent or density of hilum shadows. Four workers had slight changes on x-rays that might have been due to dust. No definite conclusions are warranted because of the small number of people, short exposure time, and dubious significance of the radiographic changes.

Estimate of Population at Risk and Prevalence of Disease

Commercial deposits of kyanite are in North Carolina and Georgia where, in 1968, about 190 employees produced kyanite (65% in processing plants, 25% in mines, and 10% in mine and plant offices). In 1978, 36 miners (open pit), 100 preparation plant workers, and 18 office workers constituted a total population of 154 kyanite workers.

Prevalence of disease is unknown.

Pathology

Small irregular nodules that may have been from mullite rather than sillimanite were observed in one furnace worker. Rabbits exposed to sillimanite did not develop silicotic type nodules. A foreign body type reaction with some fibrosis was observed.

Clinical Description—No reports

Diagnostic Criteria

Diagnosis should include a history of exposure, chest x-ray read for pneumoconiosis, and spirometry for obstructive and/or restrictive disease. The occurrence of silicotic type nodules would suggest exposure to mullite and/or cristobalite or some other silicate. Diagnostic criteria are not generally accepted as there is no well defined disease associated with kyanite minerals.

Methods of Prevention

Keep exposures low. The greatest danger is from mullite and cristobalite which form when kyanite is heated to greater than 1000°C.

Research Needs

The effects of exposure to kyanite minerals themselves are unknown. If chest x-ray records of past and current workers are available (as in North Carolina), they should be examined for pneumoconiosis.

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ISOLATED GROUP STRUCTURES (SiO₃)₆¹²⁻

The three silicate minerals considered here are beryl, cordierite, and tourmaline.

Definition

Beryl (a beryllium-aluminum silicate): No disease has been associated with exposure to the ore. Berylliosis (see Beryllium disease in this section) is commonly designated in pneumoconiosis; in actuality it is a systemic poison affecting many organs. The etiologic agent is thought to be beryllium rather than the silicate. Acute berylliosis resembles chemical pneumonia. Chronic berylliosis resembles chronic sarcoidosis.

Cordierite and tourmaline: No identified disease entity.

List of Causative Agents

Definite: Metallic beryllium, simple salts of beryllium, complex silicates of beryllium.

Probable: ---

Possible: ---

List of Occupations and Industries Involved

Beryl is a common and widely distributed mineral. It usually occurs in granitic rocks of pegmatites; it is also found in mica schists and is associated with tin ores. Prior to 1935, beryl was mined as a by product of mining other minerals like feldspar and mica. As late as 1960, 20% of domestic production was still obtained as a by-product. In 1974, domestic beryllium ore

was produced at only one site in Utah. Consumption of ore over the past few years was 7.8-10.4 thousand short tons, and imports were from 1.4-4.9 thousand short tons. Since 1969, when the plant in Utah was completed, the Utah deposit has increased the domestic source of beryl ore.

Cordierite is frequently found in steatite clay and is used as a gemstone. Tourmaline is commonly associated with china clays and granite pegmatites. It is a semi-precious gem and is used in the manufacture of pressure gauges.

Epidemiology—No studies.

Estimate of Population at Risk and Prevalence of Disease

There is only one active bertrandite mine (in Utah), so the population at risk for the ore is quite small. Prevalence is unknown. The risk of berylliosis is in the refining of beryl and the subsequent use of beryllium.

Pathology

There are no reports in humans, but long-term exposures of rats and monkeys are said to result in lesions consistent with beryllium disease.

Clinical Description—No reports

Diagnostic Criteria

No disease entity. Berylliosis is not considered in this chapter. (See "Beryllium Disease" in this section.)

Methods of Prevention

The risk of disease from beryl is unknown.

Research Needs

Workers at the new beryl mine in Utah should be followed for any signs of beryllium disease.

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CHAIN STRUCTURES ($\text{Si}_2\text{O}_6^{4-}$ or $\text{Si}_4\text{O}_{11}(\text{OH})$)

The pyroxenes and amphiboles form chains bound together by covalent oxygen bonds. The crystallographic, physical, and chemical properties of the two groups are similar. The crystals of both are lath or needle shaped and in some cases, fibrous. The pyroxene crystals, however, are commonly stout prisms, whereas amphiboles tend to form elongated, often acicular crystals.

Pyroxene Group (SiO_3)²⁻, (Mg,Fe)SiO₃

None of the pyroxenes is mined in great quantity. Augite is the most common pyroxene, occurring in many igneous rocks, but apparently only spodumene and wollastonite are commercially mined.

Spodumene, a comparatively rare mineral, is one of the commercial sources of lithium. Lithium is used in grease, ceramics, storage batteries, air conditioning, and as a welding flux. Lithium is extracted by sulphating the ore and heating the leached sulfate with ammonium fluoride and ammonium sulfate and then treating with CO₂ and ammonia. Lithium compounds are toxic to the kidneys. The major source of spodumene is in North Carolina. Located in at least eight pegmatites, the spodumene on average constitutes 20% of the rock. The rest is quartz (32%), muscovite (6%), feldspar (41%), and trace minerals (2%).

The greatest hazard in the open pit mines is from silica and not from the spodumene itself. There are no epidemiological, pathological, or clinical studies. There is no described disease, and the population at risk is quite small.

Wollastonite

Definition

Wollastonite is calcium metasilicate with an acicular crystalline shape. Particle lengths may average 7 to 15 times the diameter. There is no known disease associated with exposure.

List of Causative Agents

In New York State the wollastonite deposit is interbedded with iron garnet and iron diopside. Limestone is also likely to be present.

Definite: ---

Probable: Wollastonite, if a disease is found.

Possible: —

List of Occupations and Industries Involved

Wollastonite is used in the ceramic industry; in paint and bonding cement; as an extender for asbestos, or replacement for nonfibrous materials in brake linings, cements, adhesives, urethane, rubber, caulking compounds, phenolics, vinyls, epoxies, plastics; in fiberglass yarn, glass, insulation for electronic equipment and thermal insulation such as mineral wool; as a filler in floor tile, cements, and plastics; in laminates, athletic field markers; marking crayons; matches; mild abrasives; oil filters; wallboard; surface coating of bricks and clay sewer pipe.

Epidemiology

The miners and millers producing most of the wollastonite in the United States were recently studied by NIOSH (1). An unpublished environmental study was performed in 1964 by the New York State Division of Industrial Hygiene. Airborne fibers had a median diameter of 0.22 μm (0.2-5.2) and a median length of 2.5 μm (0.3-41). Mean fiber counts (LM) from the two studies averaged 1.4 and 20.2 fibers/cc in the mine and mill respectively. Less than 2% free silica was found in bulk samples (1)(2).

In the prevalence study, 87 current employees and five ex-employees were administered a respiratory questionnaire, chest x-ray, physical examination, and spirometry (and diffusion capacity for workers ≥ 15 years worked). There was no association of years worked with any adverse effects on health from these examinations. Thus no adverse findings were observed in this study of wollastonite miners and millers, except perhaps an increased prevalence of industrial bronchitis in smokers and ex-smokers. While the population was small (only 13 workers had worked 20-25 years and 24 had worked 15-19 years), there was no evidence of any effects on symptoms, x-ray, or pulmonary function that suggested wollastonite, at these exposure levels,

was acting like asbestos. Since wollastonite has only been mined for 20-30 years, the exposure history was short. The population was barely adequate for morbidity and was too small and had too short an exposure to assess possible carcinogenic effects.

Estimate of Population at Risk

It is not possible to estimate the exposures of workers using the finished product. The mines and mills producing most of the product are in New York state, and comprise 90-100 workers. The prevalence of work-associated disease is, to date, zero.

Clinical Descriptions

There are no pathological or clinical descriptions of any health effects associated with wollastonite.

Diagnostic Criteria

No disease entity has been identified. Based on morphological characteristics of wollastonite, the criteria that should be applied are those of pneumoconiosis and specifically asbestosis.

Methods of Prevention

There are at present no reports of disease.

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Amphibole Group (Si_4O_{11})⁶⁻ $\text{Ca}_2(\text{Mg,Fe})_2\text{Si}_4\text{O}_{22}(\text{OH})_2$

The amphibole mineral family is similar to the pyroxenes. The amphiboles readily break lengthwise. This does not fully explain the asbestiform nature of certain amphiboles, for there are varieties that are nonasbestiform, and other varieties form crystals that are roughly equidimensional (hornblende). Other factors of possible importance in the formation of asbestos

fibers are the substitution of aluminum for silicon, pressure and temperature conditions, rates of cooling or heating, and trace element concentrations during formation. The major asbestiform varieties of minerals used for asbestos are chrysotile (a serpentine) and the amphiboles tremolite-actinolite, cummingtonite-grunerite (commercially known as Amosite), anthophyllite, and crocidolite. These silicates are discussed in the separate chapter on asbestos.

Clay minerals called palygorskite (attapulgites) are complex hydrated magnesium silicates that are usually fibrous and have a structure similar to the amphiboles. They will be discussed with the montmorillonite minerals in fuller's earth. Sepiolite and meerschaum are also hydrated magnesium silicates with a similar amphibole structure. However, since they too have the adsorptive properties of fuller's earth, they will also be discussed with the montmorillonite clays.

SHEET STRUCTURES (Si_2O_5)²⁻

The minerals in this group are important for several reasons. They are products of rock weathering and, therefore, comprise the bulk of soil constituents. The structural unit of this group is the siloxane sheet which exhibits a platy or flaky habit, prominent cleavage, softness, relatively low specific gravity, and the flexibility of cleavage lamellae of these minerals. The kaolinite members of this class of silicates exhibit excellent cleavage, easy gliding, and a greasy feel as in pyrophyllite and talc.

In the true micas, the sheet-cation-sheet bonds are stronger, layers are more firmly held together, ease of gliding is diminished, hardness is increased, and the greasy or slippery feeling is lost. Brittle micas result from further chemical changes.

Minerals with a sheet structure comprise the principal constituents of clay, which is composed primarily of hydrous aluminum silicates. The most common clay minerals belong to the kaolinite, montmorillonite, attapulgite, and hydro-mica groups, and occur in varying proportions. In the discussion of sheet structures we will discuss the pure mineral. It must be remembered, however, that there may be significant proportions of "impurities" in the clay minerals. We will also discuss the known health effects of clay. Because of the complicated chemical composition of clay and clay minerals, the principal chemical components in clay are listed:

1. **Silica**—Free silica occurs in most types of clay.

2. **Alumina**—Alumina (Al_2O_3) occurs in clays in the form of clay minerals, feldspars, mica, hornblende, tourmaline. Other clays may contain alumina as gibbsite, diaspore ($AlO \cdot OH$) or a colloid.

3. **Alkali-bearing minerals**—The chief alkalis in clay occur as silicates or aluminosilicates (feldspars, micas, hydrous micas), adsorbed cations, and soluble salts (K_2SO_4 , Na_2SO_4 , $NaCl$).

4. **Iron compounds**—The principal iron compounds in clay include ferric and ferrous oxide, magnetic iron oxide, iron sulfite, iron carbonates, ferrous and ferric hydroxides, ferrosilicates, ferroaluminosilicate, ferrous aluminate, soluble iron salt (ferrous sulfate), and chlorites.

5. **Calcium compounds**—The chief calcium compounds in clay include $CaCO_3$ (as calcite or aragonite, limestone), and calcium and aluminosilicate. Gypsum ($CaSO_4 \cdot 2H_2O$) and apatite (crystalline calcium phosphate) occur in lesser amounts.

6. **Miscellaneous compounds**—Compounds of less frequent occurrence include barytes ($BaSO_4$), celestine ($SrSO_4$), magnesite ($MgSO_3$), dolomite ($MgCa(CO_3)_2$), chlorites, spinel, cordierite, rutile (TiO_2), chromite, manganese oxide, pyrite, fluorspar, topaz.

The principal minerals in clays are the following:

1. **Primary minerals**—in clays derived from igneous rocks, quartz, feldspars, and micas are the most important; olivines and pyroxenes may also be present.

2. **Secondary minerals**—clay minerals of the kaolin and montmorillonite group, chlorites, vermiculites, and hydrous micas occur commonly. Under acid conditions, the granite igneous rocks form kaolin minerals; under alkaline conditions, they can form montmorillonite minerals.

Single Layer Group

Trivalent Cations (Kaolin)

Definition

Kaolinosis is a pneumoconiosis produced by kaolin (china clay). The pneumoconiosis as seen on chest radiographs is mainly nodular or massive fibrosis of the lungs. Symptoms are dyspnea

on exertion and productive cough. Pulmonary tuberculosis and emphysema are often found if there is also a history of long exposure to kaolin, with at least part of the history involving high exposure levels. A benign pneumoconiosis is more commonly seen on chest radiographs. The characteristic finding in the benign form is a fine discrete nodulation throughout both lungs, without significant fibrosis, associated symptoms, or impairment of pulmonary function.

List of Causative Agents

Definite: Kaolin

Probable: In some instances there has probably been silica exposure, so free silica is a probable causative agent.

Possible: For kaolin in the United States, silica may only be a possible causative agent, because U.S. kaolin is secondary in origin and has less (possibly no) free silica with it. Progressive massive fibrosis develops only in the presence of tuberculosis infection.

Kaolin is known to be a good adjuvant to immune reaction and to actively adsorb antigens. It has thus been proposed (without evidence of its occurrence in man) that kaolin particles with attached antigens might localize an antigen-antibody reaction.

The causative agents then are a large kaolin load in the lungs, with quartz or tuberculosis infection important in at least some cases, and immunological factors possibly playing a role.

List of Occupations and Industries Involved

The leading consumer of kaolin is the paper industry where it is used to fill and coat the surface. Kaolin is used as a filler in both natural and synthetic rubber, as a paint extender, a filler in plastics, in the manufacture of ceramics (whitewares, wall tile, insulators, refractories). Kaolin has a wide variety of other uses for which the tonnage requirement is small: ink, adhesives, insecticides, medicines, food additives, bleaching, adsorbents, cement, fertilizers, cosmetics, crayons, pencils, detergents, porcelain enamels, paste, foundries, linoleum, floor tiles, textiles. Probably the only significant exposure occurs in the processing of kaolin when the product is dry.

Epidemiology

Epidemiologic evidence to date:

1. Kaolin does produce pneumoconiosis as determined by chest x-ray and work history. The

prevalence of complicated pneumoconiosis is low and is probably due to very high exposures in the past.

2. Simple pneumoconiosis does not correlate with disability. Complicated pneumoconiosis is associated with severe disability; it can cause death and can occur in the absence of any evidence of quartz exposure and/or pulmonary tuberculosis (although it is possible both occurred).

3. The latent period for pneumoconiosis is generally greater than 15 years.

In Georgia none of the silicon dioxide in the kaolin was in the form of free silica (2); refining the kaolin did not change the chemical composition, only the physical state. Georgia kaolin is secondary in origin and is, therefore, almost completely pure and free from grit, mica, and other accessory minerals. The particles are small (96% are less than 43 μ and 49% less than 2 μ), but because the particles tend to clump together, the dust itself does not approach this particle size distribution. The highest exposure occurred when the kaolin was dry—in the bagging and car-loading operations. Prior to 1940 a "dry process" was used, and dust concentrations reached as high as 2 bpcf (2 billion particles per cubic foot). Since 1940, a "wet process" has been in operation, with bagging and car-loading dust concentrations generally being kept below 50 mpcf (2).

There were no cases of active pulmonary tuberculosis or neoplasms in any of these U.S. workers (2). There were 44/1130 (3.9%) classified as having some degree of pneumoconiosis: 31 (2.7%) had Stage I, 7 (0.6%) Stage II, and 6 (0.5%) Stage III. In Stage I, or simple pneumoconiosis, the roentgenograms showed fine discrete nodulation (1-2 mm) generally distributed throughout both lungs. Stage II had the same fine nodulation of Stage I, plus some small confluent shadows in the upper lobes. In Stage III pneumoconiosis there was fine nodulation in the lower lobes and massive conglomerate fibrosis of the upper lobes. All with Stage III had worked longer than 20 years and in the highest exposure areas (car-loading and bagging). Of the 44 with some degree of pneumoconiosis, 2 had worked in the kaolin industry less than 10 years, 23 had worked 10-20 years, and 19 had worked longer than 20 years. Rates were not given.

Workers with Stage I and II pneumoconiosis had no symptoms, and there was little

tendency for progression over 3-12 years (when x-rays were available). The fibrotic lesions of Stage III had been gradually progressive over the 3-12 years that past x-rays were available. The lesions resembled PMF in some Welsh coal miners and were associated with disabling symptoms and very high dust exposure. The author suggested the combination of heavy kaolin dust exposure and tuberculosis produced the fibrosis. Several of the men with Stage III pneumoconiosis had cough and dyspnea on exertion and had been transferred to jobs requiring less activity. The majority of the lung changes (Stage I) were not associated with any decreased function. The author stated the prevalence of lung disease was no different than in the general population.

This was the first epidemiological study of kaolin workers (2). A standardized questionnaire and a known scheme for roentgenographic interpretation of pneumoconiosis were not used, and smoking histories were not available. Thus one cannot evaluate the severity of the effects, nor compare them with other populations. Emphysema and progression of the pneumoconiosis were seen in workers with massive fibrosis. The author tried to build a case for the combination of tuberculosis and heavy dust exposure as the causative factor in those cases with PMF. The evidence, however, was circumstantial and could not prove causation. Whether [the author's assertion that] reduced dust levels over the last 15 years will cause kaolin pneumoconiosis to disappear should be investigated. In this population there was no known free silica exposure.

If a calcining process is used in treating kaolin, it is converted to mullite, silica alumina spinel, and cristobalite. Lesser, Zia, and Kilburn reported that total airborne dust samples from a bagger, bulk loader, and calcine operator in a Georgia kaolin mill had free silica concentrations of 1.04%, 1.2%, and 1.1% in 1976 (6). Threshold limit values and time-weighted-average concentrations were not calculated, however.

Warraki and Herant took chest x-rays of 914 men working in an Egyptian industrial plant processing kaolin (14). The clay was dug and brought to the factory where it was ground and sieved in a closed chamber. The ground dust was then mixed with water to form the clay used in the manufacture of chinaware, refractories, and ceramics. Grinding and sieving were the dustiest operations. No quantitative estimate of exposure was available. Analysis of bulk samples revealed

that all particles were less than 3.4 μm , and that 83-86% of the dust was potassium aluminum silicate with 1-2% free silica.

The prevalence of pneumoconiosis (ILO 1950 classification of pneumoconiosis) was 0% (0/397) in those working less than 15 years, 1% (4/326) in those working 15-20 years, and 1% (2/191) in those working greater than 20 years. In the group working 15-20 years, there was one each of category 1, 2, and 3 simple pneumoconiosis, and one case of PMF who also had active TB. In the greater-than-20-years-worked category, both cases were classified as PMF. There was poor correlation of clinical and radiographic findings, except for one of the cases of PMF, and there was no progression in radiographic appearances over 2½ years. Four of the workers with pneumoconiosis had dyspnea and productive cough. Except for two with category 2 pneumoconiosis, the ability to work did not seem to be affected. The symptoms of the one smoker were thought to be due to smoking. The prevalence of adverse x-ray findings and respiratory symptoms was low. There was not enough information provided on how symptoms were evaluated and whether they were related to smoking. Using the author's method for measuring the health of the population, there was no apparent hazard.

Sheers conducted a survey of 1,394 men employed by one company in England which produced over 75% of the total product of the China clay industry (12). The study population was divided into exposure groups; no environmental data were available. There were no cases of kaolinosis in men with less than 5 years employment. Among the 255 workers with continuous high exposure, 32 (13%) had kaolinosis. Except for one individual in the 25-34 year age group (and 15-24 year exposure group), all cases were over 34 years of age. Prevalence was 6% (9/153) in those working 5-14 years; it rose to 23% (23/102) when the number of years worked was greater than 15 years. In the workers with intermittent exposure to kaolin dust, the overall prevalence of pneumoconiosis was 5% (16/298). The prevalence was 3% (7/244) in those with 7-24 years exposure, and 18% (9/54) among those with ≥ 25 years exposure.

The rate of massive fibrosis was lower in this population than in Egypt or the United States and was attributed to the lower prevalence of pulmonary TB and the high rate of preventive

antituberculosis chemotherapy given the men in this survey. The severity of symptoms was low, and there was no conclusive evidence that disability was caused by kaolin.

These are the only three epidemiological studies of kaolin workers reported in the literature. The overall prevalence of radiological change was low:

Simple Pneumoconiosis

U.S.A. (2)—13/1130 (1.3%)

Egypt (14)—3/914 (0.03%)

England (12)—36/553 (7.7%)

Complicated Pneumoconiosis

U.S.A (2)—6/1130 (0.5%)

Egypt (14)—3/914 (0.03%)

England (12)—12/553 (2.2%)

Symptoms and disability were not associated with simple pneumoconiosis but were with complicated pneumoconiosis. Progression to complicated pneumoconiosis was thought to be due to the combined effects of kaolin and pulmonary TB. Although environment levels were not measured in any of these studies, they appeared to be high.

These studies have several deficiencies:

1. No smoking histories were taken, so the potential for synergistic effects with smoking are not known.
2. There were no measures of functional loss; i.e., there was no measurement of lung function. Thus, we cannot objectively assess disability, nor assess the correlation of x-ray findings with disability. The assessment of disability had apparently been done on the basis of clinical findings and symptoms, but the methodology was not given.
3. Exposure was not measured; in many cases it was apparently high, at least for the older workers. Recently, dust levels have been reduced by the introduction of wet methods, exhaust ventilation, enclosure, and vacuum cleaning. In the United States, these measures have proven successful in reducing the amount of dust seen in the plants.

With these caveats in mind, the following conclusions apply:

1. The major symptoms are dyspnea on exertion and productive cough; these occur sometimes in workers with progressive massive fibrosis.
2. Normal pulmonary function would be expected, except in workers with PMF, in which case there is both fibrosis and emphysema, i.e., both obstruction and restriction.
3. The prevalence of pneumoconiosis by radiographic appearance is low and generally occurs after greater than 15 years exposure. The range of abnormal opacities is similar to that seen in coal workers' pneumoconiosis. A small proportion of workers with a high exposure at an early age and who continued to work, developed PMF with emphysema and in some cases, severe disability. There is some evidence that the development of these cases may be a thing of the past.

Estimate of Population at Risk and Prevalence of Disease

In 1972, 5,317,637 tons of kaolin were produced and sold in the United States. In 1978, the number of workers mining and preparing various kinds of clay is listed, as well as the grand total which includes office workers, underground and aboveground workers, and preparation plant workers. The latter three groups are at greatest risk.

	Underground Mining	Above Ground	Preparation Plants	Grand Total
Fire Clay	144	380	1,049	2,100
Common Clay	17	3,182	7,795	12,783
Clay, ceramic, and refractory. Not elsewhere classified.	20	68	112	243
Total	181	3,630	8,956	15,126

The prevalence of the disease is not known but based on the U.S. study, is less than 2%. Significant impairment should be less than 1%. These estimates of prevalence assume dust exposures have not increased.

Pathology

Kaolin: There are five autopsy reports of advanced pulmonary fibrosis in kaolin workers reported in the literature (2)(4)(7).

One case from England was in a 45-year-old man who had bagged kaolin powder for 28 years

and had severe dyspnea (4). Autopsy revealed extensive caseous tuberculosis and emphysema. The pleura and nodular lesions were similar to that seen in silicosis. The lungs contained about 18 gm of dust that was 85% kaolinite and 15% amorphous silica.

Two cases were reported from a kaolin processing plant in South Carolina (7). Soda ash, trisodium phosphate, and sodium pyrophosphate were sometimes added to the kaolin. The men were 36 and 35-years-old and had worked for 17 and 21 years respectively. Their chest x-rays were similar to that seen in silicosis. Gross examination of both lungs revealed emphysema, fibrous nodules, and thickened pleura.

Edenfield reported two cases in Georgia (2). Both were Negroes, aged 44 and 39, with 23 and 17 years exposure respectively. Both had severe dyspnea, and the lesions in their lungs resembled the massive fibrotic lesions seen in South Wales coal miners. Large areas of the lung were replaced by dense fibrosis; in other areas the alveoli were filled with macrophages containing kaolinite particles 1-2 μm in diameter. Both had numerous pleural adhesions and emphysematous blebs. Upper portions of the lungs were almost solid with massive lesions of dense collagen; adjacent satellite nodules of fibrosis and emphysema were evident in the remainder of the lung tissue. Dust and dust-laden macrophages were in alveoli, among collagen fibers, and around bronchioles and blood vessels.

These cases of kaolinosis were not those of a "benign pneumoconiosis." Where clinical evidence was available, the disability (dyspnea and cough) was severe. Permanent destruction of the alveolar walls was observed, as well as collagen fibrosis and permanent scarring of the lung. Exposure was high and over a long time period. Whether tuberculosis was a necessary factor in the progression to massive fibrosis was not answered by these data.

Ruttner, Spycher, and Sticher reported a case of diffuse interstitial fibrosis resembling asbestosis in a 70-year-old woman exposed to small amounts of mica, kaolin, and feldspar for 14 years (11). Chemical analysis of her lung revealed 13% of the dust was these 3 minerals. Quartz content was 7%; no asbestos was found. The author suggests the platy shape of mica, kaolinite, and feldspar act similarly to the fibers of asbestos to produce the diffuse fibrosis.

Thomas reported a case of silico-tubercu-

losis in a Cornish china clay worker who had worked for 20 years in the mill and for 5 years had trucked dry china clay from the drying kilns to the mill (13). He may have been exposed to silica for the 3 years he worked grinding china stone and feldspar. China stone may contain up to 30% free silica; china clay contains less than 3% free silica.

Lesser, Zia, and Kilburn report autopsy and lung biopsy findings on 2 patients selected from hospitalized patients with roentgenograms consistent with pneumoconiosis and occupational exposure to kaolin (6). They had not been exposed to asbestos or quartz. The first patient was 54-years-old, had 20 pack-years of cigarette smoking, a negative tuberculin test, and a 4 year history of working as a kaolin sacker in the 1940's. The second patient was 67-years-old, had 60 pack-years of cigarette smoking, a negative tuberculin test, and 30 years of kaolin exposure. The diagnosis of these 2 patients (particularly the first one) was consistent with silicosis and suggested an exposure to high concentrations of free silica and/or cristobalite. Their clinical description follows.

Clinical Description

Hale et al. reported the clinical findings of six kaolin workers with x-ray findings of pneumoconiosis (4). In the cases where massive fibrosis (coalescence) was seen on the chest x-ray, there was also dyspnea and productive cough (without blood), and often there was chest tightness, clinical signs of emphysema, and reduced vital capacity. In several of the cases, the severity of the symptoms increased rapidly. In the cases where there was no massive fibrosis, the presence of symptoms and disability was variable.

Lynch and McIver briefly reported the clinical history of the two South Carolina workers exposed to kaolin (7). Both died having "advanced pneumoconiosis with infection." In both cases their most recent exposure to dust was considered to be nonhazardous, but their initial exposure was high (and occurred when both men were in their teens). Although this suggested progression can occur after high exposure, exposure at the time of these workers' deaths was not known and may have been high by today's standard. There was no chemical analysis of the lung for kaolin or free silica. Total dust from airborne samples taken in 1976 from a South Carolina kaolin mill (2 bagger samples) revealed a free

silica concentration of 1.04% and 1.01%, which was above the TLV in both cases (6).

Lesser, Zia, and Kilburn described 9 hospital patients with roentgenograms consistent with pneumoconiosis (2 with massive conglomeration) and an occupational exposure to kaolin from work at a firebrick factory (6). Their mean age was 64 (54-73) and they had worked an average of 19 years (2-48). Two were nonsmokers and 4 had restriction (VC less than 60% of predicted). All had obstruction: FEV₁/FVC ratio ranged from .25 to .70. Average percent predicted diffusing capacity was 62% (35-100%). Environmental samples from a typical Missouri firebrick factory (and presumably similar to jobs held by the 9 patients at an earlier time period) suggested they had been exposed to kaolin, free silica, and cristobalite. Some workers' exposure to free silica could have been as high as 4.5% with TWA levels frequently above the TLV (respirable air samples). A single clay sample had 4.5% free silica. Cristobalite levels were as high as 8.9% in air samples and 15% in settled dust samples.

Diagnostic Criteria

The criteria for diagnosis of kaolinosis are nodular mottling on chest x-ray and a history of exposure (at least greater than 5 years and generally greater than 10 years).

Complicated pneumoconiosis from kaolin exposure may look similar to PMF in coal and hematite miners, or it may look more like silicosis (without the characteristic fibrosis in the hilar glands). Simple pneumoconiosis looks similar to any of the other pneumoconioses that primarily have rounded opacities. Although reductions in VC and DL_{CO} have not generally been reported, this finding (in complicated pneumoconiosis) would be expected.

Methods of Prevention

Reduction of exposure, particularly of free silica and cristobalite.

Research Needs

Kaolin (and/or accompanying silica) is known to produce silicosis, and the population at risk is substantial. Early prevalence studies did not report excessively high rates of pneumoconiosis, but some progressive massive fibrosis was present. A recent study reports (hospital) cases are still occurring. None of the studies report environmental exposures, so dose-response rela-

tions cannot be estimated. The possible presence of silica and/or cristobalite increases the hazard. A prevalence study using spirometry in addition to chest roentgenograms should be conducted in the kaolin industry.

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Divalent Cations—Serpentine (Chrysotile, Antigorite)

Divalent cations can replace the aluminum ions in kaolinite. When the ions are magnesium, serpentines are formed. Two important minerals are in this group—chrysotile and antigorite.

Chrysotile is the fibrous variety of serpentine and is a major source of asbestos. It is discussed in the chapter on asbestos. *Antigorite* is the platy variety of serpentine. Serpentine, as a rock name, usually refers to rocks containing antigorite. Serpentine is a widely distributed, common mineral and is an alteration of magnesium silicates (especially olivine, pyroxene, and amphibole). It is frequently associated with magnetite, chromite, magnetite, and sepiolite.

Rohl, Langer, and Selikoff recently investigated environmental asbestos pollution as a result of using crushed rock from a Maryland quarry (2). The bulk of the serpentine rock was antigorite, in both platy and fibrous forms, with veins or lenticular bodies of chrysotile, tremolite, deweylite, talc, anthophyllite, chlorinozoizite, peninite, and other silicate minerals. Chlorite commonly replaced antigorite. This type of crushed serpentine rock has widespread and large-scale use in the United States. The rock from the Maryland quarry has been used for road metal, base course, and resurfacing of highways, parking lots, and driveways; as concrete aggregate and other materials in the construction industry; and as filler-binder for asphalt. Air samples taken in the vicinity of roads paved with the serpentine rock showed concentrations of chrysotile about 10^3 times higher than concentrations typically found in urban ambient air in the United States.

Frank et al. examined the effect on cell growth of extracted chrysotile and ground rock samples of platy serpentine from the Maryland quarry (1). The ground serpentine had no effect. The extracted chrysotile was cytotoxic at 72 hours, but less so than when compared to UICC

standard reference samples of Canadian chrysotile.

There is, at present, no other data on biological effects of serpentine rock. A current NIOSH project is investigating the mortality of crushed-stone workers. This is an important study because of the potential exposure to asbestiform minerals and the large group of potentially exposed persons (both in the community and at work).

Chlorites are a group of minerals with wide variations in chemical composition due to substitution of aluminum, ferrous and ferric iron for magnesium in the talc and brucite layers, and of aluminum for silicon in the siloxane layer. Chlorite is a common mineral, forming as an alteration of iron or magnesium silicates (pyroxenes, biotite, garnet, idocrase). It is not mined as such, and there are no medical data on the chlorites.

There are no clinical descriptions, pathology reports, or epidemiological studies of the divalent cation group (except for the asbestos mineral chrysotile). There is no described disease, no diagnostic criteria; exposure is to mixed dusts.

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Double Layer Group

Pyrophyllite

Definition

Pneumoconiosis but without characteristics specific to pyrophyllite.

List of Causative Agents

Definite: ---
Probable: Silica
Possible: Talc, pyrophyllite

List of Occupations and Industries Involved

Pyrophyllite has uses similar to talc as it is used in refractories, rubber, ceramics, insecticides, plastics, paint, and roofing. Minor amounts are used in bleaching powder, textiles, cordage, wall-

board, and cosmetics. Commercially, pyrophyllite is classified and used as talc because of its similarity in physical properties.

Epidemiology

Of 101 pyrophyllite miners and millers in North Carolina, 35% with ≥ 2 years exposure had chest x-rays characterized by "massive tumor-like shadows bilaterally situated in the subapical region or by granular densities distributed throughout the lungs." These findings were undoubtedly due to the 25-35% quartz content of the pyrophyllite dust.

Hogue and Mallette reported on 20 rubber workers exposed to whiting (CaCO_3) about 90% of the time with approximately 10% exposure to pyrophyllite containing 65% free silica (2). Vermont talc replaced pyrophyllite for six years prior to the study. Exposure periods ranged from 10-25 years, age from 42 to 64 years. Average dust exposures for the last six years ranged from 30 to 150 mppcf (median = 50 mppcf) and were thought to be higher prior to that. None of these men complained of symptoms (dyspnea, cough, shortness of breath). There was no finger clubbing or cyanosis; six had a reduced vital capacity. One former coal miner (5 years) with 24 years in the rubber industry and an average exposure of 150 mppcf had Grade III pneumoconiosis, reduced vital capacity (68% of expected), but no disability. All other chest roentgenograms were "normal."

The pyrophyllite exposure in the rubber study was small when compared to whiting and silica and is therefore unlikely to be the causative agent in the one case of pneumoconiosis or in the cases of reduced vital capacity.

Estimate of Population at Risk and Prevalence of Disease

Pyrophyllite is mined primarily in North Carolina by about 200 miners. Several cases of silicosis have been noted in this population.

Pathology

No reports related exclusively to pyrophyllite.

Clinical Description

No reports related exclusively to pyrophyllite.

Diagnostic Criteria

The criteria for diagnosis include a history of exposure and a chest x-ray with features

characteristic of pneumoconiosis (most probably characteristic of silicosis).

Methods of Prevention

Maintain silica exposure below standard.

Research Needs

The current work force needs to be studied for the prevalence of silicosis. There was a high prevalence of disease among miners 40 years ago, but the population has not been studied since.

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Talc

Definition

The character of pneumoconiosis associated with "talc" exposure depends on the composition of the talc dust inhaled. When asbestos is the dominant mineral, the disease is characteristic of asbestos-induced disorders. When talc is associated with quartz, the reaction of the lung to quartz is modified—giving rise to localized fibrocellular lesions—and is called talco-silicosis.

Talcosis (foreign body granulomas) is pneumoconiosis caused by deposition of "pure" talc (i.e., talc free from asbestos and quartz). Granulomas have been observed in pulmonary arteries and arterioles as a result of drugs injected with talc as a carrier, and in the peritoneum, fallopian tubes, and ovaries from talc used on surgical gloves.

List of Causative Agents

Definite: Asbestos (fibrous amphiboles, tremolite, actinolite, and anthophyllite) for talco-asbestosis. Silica for talco-silicosis.

Probable: Talc for talcosis.

List of Occupations and Industries Involved

Talc is an extremely versatile mineral that has found a steadily increasing number of uses,

despite the relative impurity of most of the ores mined. Except for pure steatite grades, hand-picked platy cosmetic talcs, and a few products from wet processing plants, industrial products are really mixtures of many minerals. For example, much of the talc used by the ceramic industry is a mixture of platy talc and tremolite; most of the talc used by the rubber, plastic, and paper industry is, at best, about 90% talc with the balance being dolomite, calcite, chert, clays, serpentine, chlorite, actinolite, iron and manganese-containing minerals, and carbonaceous material. Since industry is (in general) interested in the physical characteristics of the talc rather than the chemical composition, the occupations and industries involved will include uses of both "fibrous" and "nonfibrous" talc without distinction between the two.

The principal uses of talc include: extender and filler pigment in the paint industry; coating and filling of paper; ceramic products; filler material for plastics; roofing products.

Miscellaneous uses of talc include: binders and fillers in textiles; fillers in integral foamed latex rubber backings for carpets, rugs, and parquet hardwood floor panels; filler for upholstery fabric backing and draperies; lubricant in extreme temperature range greases; use in corrosion proofing compositions; 10-15% in dry fire-extinguishing powders; loading and "bleaching" materials such as cotton sacks, cordage, rope string; cereal polishing (rice, corn, barley); bleaching agents; food odor absorber; floor wax; water filtration; leather treatment (oil absorption); joint fillers and grouts; insecticides; shoe polishes; welding rod coatings; printing inks; encapsulant for acceleration testing artillery shells up to 50,000 g., coating for iron ore pellets in direct reduction processes; source of magnesium in plant foods; pigment in white shoe polishes and white glove cleaners; dusting powder for salami; admixture for certain concretes; polishing medium for peanuts, gunpowder grains, turned wooden articles; to prevent sticking of bottle, rubber, and candy molds; and to impact a finish to wire nails and leather.

In 1977, the percentage uses of talc were 22% for ceramics, 17% for paints, 8% for paper, 6% for refractories, 5% for building materials, 5% for insecticides, 4% for toilet preparations, 2% for rubber products, and 31% for all other uses of which only a fraction are listed here (other uses number at least 100).

The most significant exposure occurs in milling talc. The exposure to talc in users is largely unknown.

Epidemiology of Talc Without Asbestos Minerals or Quartz

Descriptions of "talc" pneumoconiosis commonly resemble asbestosis or less commonly, silicosis. There is usually no description of the fiber or free silica content of the talc. When exposure is to "pure" talc (no asbestiform fibers, no free silica), there are few or no symptoms or impairment in lung function. The lack of disability together with long exposures to talc dust suggests talcosis should be designated a "benign pneumoconiosis."

Merewether reported that rubber tire workers exposed to French chalk showed "diffuse interstitial fibrosis" by chest x-ray and nothing more than "peribronchial increase in the fibrous tissue" after 30 years. Exposure ranged from 10 to 32 years. Examination of 13 additional workers with exposures of 4-1/2 months to 40 years supported the previous finding.

Hogue and Mallette reported on 20 rubber workers exposed to talc (among other things) containing no free silica, tremolite, chrysolite, chrysotile, or actinolite (18). Years worked ranged from 10 to 36 years, and for a 6-year period prior to publication of the report, exposure averaged 20 mppcf for 6 tube machine operators, 35 mppcf for 3 tube bookers, 15 mppcf for 10 tube curemen, and 50 mppcf for 1 liner reroller. None of these men had dyspnea, cough, shortness of breath, cyanosis or clubbing of the fingers. Chest x-rays were all normal, and the range of percent predicted VC was 71%-122% with a median of 105%. The authors concluded that "long exposure to talc does not appear to produce pathologic changes in the lungs."

Fristed et al. reported 5 cases of talcosis (defined by x-ray and history) in workers manufacturing inner tubes and water hoses and exposed to "Scandinavian granular talc" (11).

Quartz content of the talc as measured at the time of the study was consistently less than 1%; the percentage of needle-shaped particles 5-20 μm in length was 0% to 1.2%, and for needle-shaped particles greater than 20 μm , the percentage was 0.02% to 0.05%. X-ray diffraction analysis revealed no tremolite or other steatites. Mean concentrations of dust in the 2 inner tube departments was 61 mppcf (22-75) and 66

mppcf (32-99) and was 37 mppcf (10-121) in the water hose department.

The authors described these cases of talcosis occurring on exposure to granular talc and characterized this type of talcosis as similar to slow progressing silicosis; i.e., nodular changes with involvement and blockages of the lymphatic system and an increased risk of tuberculosis. All cases had negative tuberculosis culture tests. Crystallographic examinations of the lymph nodes showed high levels of talc and 5% quartz, which is about twice that of persons not exposed to quartz. The average latency for the development of talcosis, presumably determined by chest x-ray, was 35 years. Based on current levels, exposure was high (2-3 times the 20 mppcf TLV for talc). Past exposure could have been even higher, and there could have been intermittent past exposure to higher levels of asbestos minerals (e.g., actinolite, tremolite) and quartz. Detrimental effects on health appeared to be minimal although the description of the syndrome was meager. Smoking status of these workers was not given. Biopsy revealed fibrosis of mediastinal lymph nodes. No information was given on the population at risk, so prevalence is unknown.

Scansetti, Gaido, and Rasetti in a cross-sectional study, examined 72 Italian rubber workers exposed to talc containing no free silica or asbestiform fibers (42). They had no other dust exposure. Based on clinical examination and chest radiograph, the prevalence of bronchitis, emphysema, and pleural compartmentation was 8%, 5%, and 4% respectively. The prevalence of bronchitis was low compared to extractive industries (mining). The prevalence of bronchitis, emphysema, and abnormal radiographs increased with years worked. At least 9 workers with less than 3 years exposure had abnormal radiographs and bronchitis; all workers with greater than 16 years had abnormal radiographs. The authors stated that increased pulmonary marking developed early, and did not get any worse. However, they provided no evidence to support this assertion.

The association of radiographic and clinical findings with years worked was undoubtedly confounded by age, smoking, and free silica exposure, although no information was provided. Unfortunately, there were no environmental measurements, and the criteria used for evaluating abnormalities was inadequately defined

and so cannot be compared with other populations. It appeared, however, that effects of exposure were mild as there was no fibrosis and no reduction in respiratory function of working capacity.

Scansetti, Rasetti, and Ghemi reported a prospective study of Italian talc miners (43). The talc was not characterized but was presumed to contain no asbestos and less than 1% quartz, although on occasion free silica exposure could have been quite high. The initial group of 236 workers had an average of 4.9 years exposure; subsequent examinations of this same group were made 9.4 (n = 229), 11.6 (n = 55), and 14.6 (n = 22) years later. Bronchitis and emphysema were determined by clinical examination. Diagnostic criteria were not clear. The prevalence of bronchitis, emphysema, right heart involvement, reduced predicted VC, reduced ventilation, Tiffeneau index, and pneumoconiosis increased as years worked (and age) increased. There was a good correlation of radiographic findings and reduction in pulmonary function. The authors commented that while the incidence of abnormality was high, the severity of the disease was slight. It is not possible to determine disability from the data presented, nor is it possible to evaluate the effects of age, smoking, natural selection (the attrition rate was quite high), or dose-response relations. Further, the drillers may have been exposed to significant quantities of free silica.

Rubino et al. conducted a historical prospective mortality study of male talc miners and millers (41). Air samples had been collected since 1948, and environmental levels in the mine had been at or below the TLV since about 1950-1955 and in the mill since about 1960. The talc was from the same region as the previous two studies and contained very little asbestiform fibers. Environmental exposures to free silica in the mill were less than 1% but in the mine ranged from 1% to 18%. The highest exposure to quartz occurred in drilling (12% to 18% free silica) due to the high quartz content in the rock and inclusions. In mucking and carrying jobs the percent free silica was 1% to 3%. In this study and the previous one, some talc miners had a significant exposure to free silica. Therefore, in this study, millers were analyzed separately, and workers with any experience in the talc mines were not included in the miller category. When compared to control subjects in a nearby town,

the overall SMR was significantly less than 1 (.89 and .88 for miners and millers respectively), and there was no dose-response relation, i.e., there was no relationship of increased SMR (both overall and by cause of death) with increasing interval between first exposure and death (latency) nor with increasing cumulative exposure. Overall, miners had a significant excess of silicosis (observed/expected = 62/30.9) and silicosis with tuberculosis (observed/expected = 18/9.1).

Rubino et al. subsequently reanalyzed this data using the entire white male population as controls (40). In this comparison, SMR's for both miners and millers were elevated. Overall, the miners showed no consistent relationship with exposure. The SMR's for both miners and millers were elevated and the SMR's decreased with increasing exposure. Respiratory disease (primarily pneumoconiosis) increased with increasing exposure among the miners, but decreased with increasing exposure among the millers (as did lung cancer among the millers). Of the four cases of pneumoconiosis among the millers, 2/4 had known previous exposure to free silica, and for 1/4 previous dust exposure was not known. The latent period ranged from 29 to 41 years, duration of exposure ranged from 3 to 23 years. Thus there was no association by cause of death with cumulative dust exposure among the millers, and the association of death due to non-malignant respiratory disease and tuberculosis with exposure was attributable to quartz exposure.

Rubino et al. also examined all currently (1975-76) employed talc millers who did not have other exposures to inorganic dust and who were employed at the same location as the workers in the mortality study (40). Chest radiographs of the 43 millers showed that grade 1/0 pneumoconiosis (ILO/UICC classification scheme) appeared after an estimated cumulative exposure of greater than 160 mppcf and grade 1/1 and 1/2 after 320 mppcf. Mean duration of exposure was 22 and 29 years respectively: a mean exposure of 7.3 mppcf/year for grade 1/0, and 11 mppcf/year for grade 1/1 and 1/2.

Delaude examined French workers exposed to talc that was chemically pure and contained chlorite, calcite, traces of pyrite, quartz (less than 3.5%), and no asbestos (6). Among 94 exposed workers, 15 cases of pneumoconiosis were found; 8 with minimal radiographic signs. Mean exposure was 25 years (range of 11-36 years). Exposure in the past was high, in certain jobs as

high as 800 mppcf. One of the 15 cases had reduced pulmonary function. In smokers, the effect of exposure was increased: the prevalence of chronic bronchitis among nonexposed smokers over 40 years of age was 27%, compared to 58% for a similar group of [presumably smoking] exposed workers. The authors characterized the syndrome caused by French talc as a benign pneumoconiosis. It had none of the characteristics of asbestosis or silicosis, but was the result of very high and prolonged exposure to pure talc that in itself can "cause a ventilatory insufficiency and . . . aggravate an obstructive bronchopneumopathy." No increase in lung or pleural cancer or gastrointestinal cancer was observed although no details were given.

Katsnelson and Mokronosova compared the mortality of Russian talc miners and millers employed between 1949 and 1975 with the mortality of a comparison population from the same town (21). Cause-specific mortality was limited to death from tumors of all sites, lung cancer, and gastric cancer. Talc workers with less than 2 years exposure were put in the control population. Relative risk (R.R.) (the ratio of death rates in the 2 populations after standardization for age) was elevated in both males and females (except for lung cancer in females). The R.R. increased with age for all tumors, although the increase was greatest for lung cancer. The talc contained no tremolite, no nonasbestiform actinolite (it was present in one bedding only and then only up to 6%), and 0.2%-1.6% quartz. The main minerals other than talc were carbonate minerals (up to 42%).

The conclusions from this paper may not be correct for the following reasons:

—The control or comparison group was not defined.

—The calculation of rates may be erroneous as the denominator of the study cohort did not represent the population at risk. If the worker population at the plants had been declining over time, the cancer rates would have been overestimated. It is also not clear if the numerator for the control group was derived correctly, and if not, there could be a serious underestimate of the control cancer rate.

—There is not enough detail on the methodology used to determine whether the conclusions are valid.

El-Ghawabi, El-Samra, and Mehaseb conducted a cross-sectional study of 50 Egyptian talc

millers (9). The talc contained no free silica, but it is unknown whether asbestiform fibers were present. All environmental measurements were above the TLV. Average exposure levels in front of the mill were 68.5 mppcf (54-83, $n = 12$); behind the mill, 30 mppcf (25-35, $n = 12$); and in the package area, 92 mppcf (73-111, $n = 12$). Pulmonary function was not reduced in this population (one reduction in FVC, none for FEV₁), and symptoms did not correlate with radiographic findings. The overall prevalence of radiographic findings was high (88% for those with ≥ 15 years worked) although there appeared to be little disability associated with them.

These studies comprise the total number of epidemiological studies (performed outside the United States) of workers exposed to nonasbestiform talc with a low silica content. Pulmonary function in exposed workers with pneumoconiosis was only marginally reduced, if at all. The severity of symptoms and radiographic changes were, in general, minimal. Latency was generally greater than 20 years. Exposure was well above the standard of 20 mppcf, and in some cases quartz was present in significant quantities.

The remaining epidemiological studies were done in the United States. In 1958, 15 talc miners and 46 talc millers in Lewis County, New York were studied (31). Average free silica content of 10 samples was 1.4% (0.2-4%). Microscopic examination revealed irregular aggregates of scaly or granular particles but no tremolite. Average dust counts obtained in 1940-48 in the mill ranged from 171 mppcf to 537 mppcf (the range for single dust counts was 47 to 1090 mppcf). After controls, the mean dust counts in 1958 for the same jobs ranged from 23 to 96 mppcf (the range for individual dust counts was 13 to 113 mppcf). Levels were much lower in the mine, as average dust counts for drilling and mucking in 1958 were 1-5 mppcf. The highest individual sample was 7.5 mppcf. None of the 15 miners had pulmonary fibrosis; 2/46 millers had increased bronchovascular markings. Their average exposure was greater than 50 mppcf for 31 years worked. Two other workers with fibrosis had worked for more than 20 years at exposures greater than 50 mppcf. The authors compared these findings to talc workers exposed to tremolitic talc (this talc probably also contained anthophyllite). The Lewis County millers had a minimal degree of fibrosis (less fibrosis than the workers exposed to tremolitic talc), and the in-

idence of fibrosis was significantly lower, despite the same (and, at times greater) dust exposure and longer years worked (31 versus 19.6 years). Exposure to this nonfibrous talc produced minimal fibrosis at very high exposure levels. The authors concluded that if exposures were less than the TLV of 20 mppcf, it would probably produce no fibrosis.

In a cross-sectional study, Fine et al. administered pulmonary function tests, chest x-rays, and respiratory questionnaires to 80 rubber workers exposed to industrial grade talc and 189 nontalc exposed rubber workers (10). This study showed an increased prevalence of cough, phlegm, and wheezing in talc-exposed workers compared to nonexposed workers. There were no abnormal radiographic findings or cases of restrictive lung disease, but there was evidence of mild obstruction in those exposed compared to controls in the greater-than-10-years-worked group. There was a clear increase in symptoms in the exposed compared to control group, but it is not known whether this occurred in the less-than-10-years group, greater-than-10-years groups, or both. The characteristics of the talc used in the past were not mentioned; it could have contained both asbestos fibers and/or free silica. Exposure is not known because the reported environmental measures did not correspond to the job the exposed talc workers actually performed.

Wegman, Burgess, and Peters administered an MRC questionnaire, chest x-rays, and spirometry to talc miners and millers in Vermont in a one year prospective study (56). The talc was considered free of asbestos and free silica. In the initial cross-sectional study of 117 talc miners and millers, percent predicted FEV₁ and FVC were 97% and 104% respectively (standardized by comparison with the prediction equations of Kory et al.). Percent predicted FEV₁ and FVC were reduced in current smokers compared to ex- and nonsmokers and in the group working ≥ 20 years compared to the group working less than 20 years. Heavier smokers (≥ 1 pack/day) had a better percent predicted FEV₁ and FVC than did light smokers (less than 1 pack/day). A similar relationship was observed for MMEF and RV/TLC. There was a general tendency for percent predicted FEV₁, FVC, and MMEF to become smaller as estimated cumulative exposure (dust years and years exposed) increased. Unfortunately, this relationship was confounded

with smoking, as the group smoking longer than 20 years probably also had more cumulative exposure than the less-than-20-years smoking group. Multiple regressions with age, height, years smoked, and years employed had statistically significant associations ($p < .05$) of age, height, and years smoked with percent predicted FEV₁ and a significant association of age with percent predicted FVC. Mean percent predicted FVC for smoking or exposure category ranged from 98.7% to 108.7%; for mean percent predicted FEV₁ the range was 87.9% to 107.9%.

The prevalence of abnormal x-ray findings in this study was higher than in previous studies (6% with 2/1 small rounded opacities, 4% with 2/1 small irregular opacities, and 9% with pleural abnormalities) and was associated with years worked and estimated cumulative exposure. The authors stated that talc could be causing obstruction, but this apparent association is more likely due to smoking. This longitudinal study was too short (one year) to adequately document dose-response relationships. If anything, it showed no relationship of talc exposure (as measured by current job exposure) with changes in FEV₁, FVC, and MMEF.

Selevan et al. conducted a mortality study of Vermont talc miners and millers exposed to talc containing no asbestos and less than 1% free silica in both bulk and air samples (50). This study showed an association of pneumoconiosis with talc exposure that was well above the current TLV. Whether current exposure levels can produce the same degree of pneumoconiosis is not known. The possible interaction of cigarette smoking and talc could not be evaluated.

An unpublished prospective study of 70 Vermont talc miners is reported by Hildick-Smith (17). The talc was cosmetic grade, 90% pure, and after processing in the mill, was free from asbestos and silica. Average dust exposure was 7.6 mppcf, and average work duration was 4.6 years. This study showed that smoking talc miners exposed to low concentrations of talc for a short period of time did not differ from a smoking population not exposed to dust, and that the smoking talc miners differed only slightly from a nonsmoking population. As exposure time was short, and the population was young, the effects of long-term exposure are still not known.

In an unpublished epidemiological-industrial hygiene study of talc workers, a higher than ex-

In an unpublished epidemiological-industrial hygiene study of talc workers, a higher than expected prevalence of bilateral pleural thickening was found in a group of 299 talc miners and millers from Montana, Texas, and North Carolina, who were examined in a cross-sectional study of respiratory symptoms, lung function, and chest x-rays. Lung function parameters associated with the affected subgroup were significantly reduced. Personal respirable dust samples were collected for all jobs, and cumulative exposures were calculated. Average time worked was short; average exposure was 2.6 mg/m³. Free silica content of bulk samples was low. No fibers were observed with light microscopy. With transmission electron microscopy, tremolite and antigorite fibers were observed in the Texas talc, acicular particles in North Carolina talc, and no fibers in the Montana talc. Differences in age corrected symptom prevalences (cough, phlegm, and dyspnea) between regions, when compared by both smoking categories and exposure groups, were not statistically significant. None of the symptoms showed any consistent association with years worked or cumulative exposure. Symptom prevalence was not elevated compared to blue collar workers and potash miners. However, the prevalence of bilateral pleural thickening was elevated in workers 40 or older compared to blue collar workers and potash miners. No nonsmoker had bilateral pleural thickening. Workers with bilateral pleural thickening had lung function 10-20% below workers with no pleural thickening. They had also worked twice as long (13 years). There were no demonstrated differences in prevalence when the subjects in this study were compared to workers exposed to New York talc which contains tremolite and anthophyllite. For this sampled talc population, no association of reduced lung function with exposure was demonstrated; there were no significant increases in symptoms or pneumoconiosis, no significant reductions in lung function. After adjustments for age, height, and smoking, FEV₁ and FVC were not detectably different compared to potash miners and blue collar workers. However, flow rates at low lung volumes were 4-19% less than all of those comparison populations. The prognostic significance of the pleural thickening awaits prospective evaluation.

Estimation of Population at Risk and Prevalence of Disease

The total number of workers mining talc, soapstone, and pyrophyllite in 1978 was 144 underground, 243 on the surface, 683 in preparation plants, and 173 office workers for a grand total of 1,243. This total includes fibrous talc, which totals at least 200 workers. The number of workers exposed in secondary industries is unknown.

Pathology

In vitro tests suggest that pure crystalline talc is less pathogenic than free silica or asbestos. Inhalation experiments with animals suggest that talc may produce some pulmonary fibrosis, however, other minerals in the "talc," including quartz and asbestos fibers, probably contributed to the pulmonary injury. Several investigators have introduced talc and other particulates intratracheally into experimental animals. No significant pulmonary fibrosis developed in rats exposed to talc without quartz contamination, but in animals exposed to talc with 10% silica, an intense pulmonary fibrosis was noted. Schepers and Durkan introduced various combinations of minerals into the tracheas of guinea pigs once weekly for three weeks and sacrificed the animals up to 2 years after exposure (46). The authors concluded the basic reaction to talc, quartz, tremolite, and anthophyllite dust was an outpouring of macrophages into the alveolar spaces with phagocytosis of the particulate matter. Although the macrophages might become immobilized and, therefore not removed from the lung, no necrosis or fibrosis was stimulated unless the particulate matter was in the form of long fibers. Damage to small airways and vessels was produced by the talc exposure, but the reaction was mainly accumulations of cells with little deposition of collagen. The authors contrasted this with diffuse interstitial fibrosis which was associated with exposure to the fibrous materials. Quartz increased the pathogenic potential of the talc-asbestos mixture.

Although useful, animal exposures as described above are subject to certain limitations. In inhalation experiments, the doses used are often massive compared to usual human exposures. The introduction of the material in solu-

tion intratracheally may produce artifactual lesions. Gross and co-workers found that materials producing no lesions inhaled caused polypoid fibroblastic lesions in the bronchioles and alveolar ducts of rats when injected intratracheally (4). The stroma of these lesions consisted of reticulin fibers and dust with an occasional giant cell. The lesions disappeared after 6 months. When quartz, asbestos, or talc were injected intratracheally, similar lesions were found, but the lesions progressed to collagenous fibrosis and distortion of bronchioles. Thus experiments conducted with intratracheal injections might produce artifactual lesions not associated with the material when inhaled.

In persons exposed to talc by inhalation, gross examination of the lungs may reveal diffuse pleural thickening and fibrous adhesions of the pleural surfaces. In some cases, localized pleural plaques, which may calcify, are located on the costal parietal pleura and the diaphragmatic surfaces. The lungs themselves may contain multiple small nodular lesions less well defined than those usually seen in persons exposed to free silica. Large fibrotic masses which undergo central necrosis and cavitation have been reported. Diffuse interstitial fibrosis with cystic changes in the lower lobes may be the predominant lesion. Microscopically, pulmonary parenchymal lesions may be classified in 3 general groups.

1. There may be a diffuse interstitial fibrosis with collagen deposition in the alveolar walls and dust-laden macrophages both in the alveolar septa and free in the alveolar spaces. Bronchi and bronchioles may be distended and distorted, and normal lung architecture may be obliterated with dilated spaces lined with cuboidal metaplastic cells replacing the alveoli. Elongated brownish beaded or clubbed shaped "asbestos bodies" are often found in respiratory bronchioles or in masses of fibrous tissue in lungs with the changes just described, suggesting that asbestos played a significant role in the pathogenesis of the lung damage.
2. A second type of lesion is that of widespread, ill-defined nodules. These nodules consist of stellate collections of macrophages and fibroblasts with birefringent particles both inside macrophages and lying free. There may be some fine

reticulin, but little collagen is found in these lesions. The lesions may center on medium and small pulmonary vessels and around small bronchi and bronchioles. There is generally no diffuse deposition of collagen in the alveolar septa and no alveolar septal cell hyperplasia. Large pulmonary vessels are normal, and although there may be some endarteritis obliterans in smaller arterioles, the elastic lamina is intact and capillary circulation appears relatively undisturbed. In those lungs found to have a higher quartz content, much more pronounced and diffuse collagen deposition is found. Some of the nodular lesions may take on a partially whorled appearance resembling lesions found in classical silicosis, and vascular compromise is more pronounced. Nodules may coalesce, form large fibrotic masses, and eventually cavitate due to ischemic necrosis. Pulmonary lymph nodes containing macrophages filled with particulate material, fibrosis, and sometimes calcification may be seen in lungs with high quartz content. In patients with extensive lesions (as just described) or severe diffuse interstitial fibrosis, right ventricular hypertrophy (cor pulmonale) may be found.

3. The third type of lesion seen in the lungs of persons exposed to talc is that of foreign body granulomata. These granulomata consist of epithelioid cells and foreign body giant cells often containing birefringent crystals. Granulomata may be found in association with nodular fibrosis or isolated in the alveolar interstitium with normal thin alveolar septa intravening. They may also be found in fibrotic and thickened pleura. In persons exposed to talc by intravenous injection (see below) granulomata may be found predominantly in vessel walls.

The pulmonary pathology found in workers with inhalational exposure to "talc" varies, depending on the composition of the dust inhaled. When silica content is significant, the lesions resemble those in silicosis. When fibrous materials such as tremolite are present, diffuse interstitial fibrosis resembling that of asbestosis may be found. Whether pure mineral talc itself causes

any permanent reaction in humans is open to debate. Talc particles which penetrate into the airspaces beyond the level of terminal bronchioles are phagocytosed by macrophages. If the total dust burden is not too high, migration of the macrophages into the alveolar spaces and ultimately into the lymphatic system may not leave any (essentially) permanent changes in the lung parenchyma. Where dust burdens are higher, all dust bearing macrophages may not be cleared, and focal collections of macrophages—some coalescing into foreign body giant cells—may result. As usual, individual differences in susceptibility probably affect the exact nature of the response. There is strong evidence that the reaction to dusts containing a predominance of the mineral talc is more cellular and less fibrotic than that to free silica or asbestos fibers. Pure talc alone may be capable of inciting a foreign body granuloma although granulomata are also seen in classical silicosis.

Clinical Description

The development of pathologic changes in the lungs and subsequent symptoms depends upon the intensity and duration of exposure as well as individual differences in reaction to dust. Symptoms in talc workers generally take longer to develop than in persons exposed primarily to asbestos or silica. The earliest symptom appears to be chronic cough which may be accompanied by production of small to moderate quantities of clear sputum. This may be a manifestation of nonspecific "industrial bronchitis" and is seen most often in workers who smoke cigarettes. As the disease progresses, dyspnea on exertion becomes the most common feature. Wheezing is usually not a prominent feature but may be present during episodes of acute bronchitis. Severe dyspnea is more commonly associated with the diffuse interstitial fibrosis pattern than the nodular type but may be seen in patients with conglomerate lesions.

Early in the course there may be no abnormal physical signs. With the diffuse interstitial fibrosis pattern, breath sounds may become harsh, chest expansion diminished, and basilar crepitations may be present. As impairment progresses, resting tachypnea, worsening with exercise, and peripheral cyanosis may develop. If cor pulmonale is present, the usual signs of this condition including peripheral edema, elevated venous pressure, and gallop rhythm on auscultation of the heart may be present. Clubbing of the fingers is commonly present at this stage.

For those with nodular type disease, phys-

ical examination may remain normal, but when confluent conglomerate lesions are present, dullness and diminished breath sounds occur over the lesion. Generalized limitation of chest expansion, decreased breath sounds, and prolonged expiratory time may also be present.

The radiographic appearance is variable. Patients may have completely normal chest x-rays and yet be found to have numerous granulomatous lesions in the alveolar interstitium. Diffuse reticulo-nodular opacities often predominate in the mid zones. In some instances, the lesions may be relatively discrete, rounded opacities 3-5 mm in diameter, whereas in others, the shadows may be more linear or irregular and occur predominantly in the bases. The radiographic appearance probably varies between that of classical silicosis and asbestosis, depending on the predominance of free silica or asbestos in the dust inhaled. Occasionally, the shadows may be diffuse, small nodules simulating miliary tuberculosis. These shadows may be due to miliary granulomata with little intervening interstitial fibrosis. As the condition advances, nodular opacities may coalesce and eventually form large confluent shadows with irregular borders. These lesions may eventually cavitate. Pleural thickening is common in workers exposed to talc. It may take the form of diffuse thickening (especially in the lower zones), obliteration of the costophrenic angles, and in some instances pleural plaques located on the diaphragms or parietal thoracic pleura. Calcified pleural plaques were commonly seen on x-ray in cases where "asbestos bodies" were present in the lungs.

The radiographic appearance in advanced disease may resemble that in end-stage silicosis with progressive massive fibrosis, loss of volume, and over-distention in the remaining lung. Advanced interstitial fibrosis resembling asbestosis may result in obscuration of the cardiac borders, loss of volume, and cystic changes, especially in the lower zones. Signs of cor pulmonale with right ventricular prominence and enlarged central pulmonary artery segments may also be present.

Early studies of pulmonary function in talc workers frequently did not take into account the effects of smoking and thus are difficult to interpret. Many of the studies also did not adequately document the asbestos and silica content of the talc. Pulmonary function testing may reveal normal function in those with minimal involvement on chest x-ray. In those with significant inter-

stitial fibrosis, a diminished FVC and FEV₁, and/or decreased DL_{CO} may be the first manifestation. With more advanced disease, hypoxemia during exercise and later at rest may be found. In those, the predominantly nodular disease function impairment may be less severe. Progression, however, may occur and result in significant restrictive and perhaps obstructive lung disease, especially when conglomerate lesions are visible on chest x-ray. A subtle gas exchange impairment may progress to produce clinically significant blood gas abnormalities in advanced cases.

There are no other laboratory examinations which are specifically helpful in the evaluation of patients with pneumoconiosis due to the exposure of talc. Routine examinations such as complete blood counts provide no specific information (but, of course, may be useful in the management of the patient). Electrocardiograms are usually normal, but in cases with severe disease and cor pulmonale, signs of right ventricular hypertrophy may be present. Lung biopsy may establish the diagnosis in unusual cases but should seldom be necessary.

The development and progression of pneumoconiosis due to talc depends upon the intensity of exposure and individual differences which are not well known at the present time. More complete discussion of possible immunologic and pulmonary defense mechanism differences accounting for variations in response to inhaled dust have been given in other chapters on the pneumoconioses. In general, pneumoconiosis associated with talc tends to progress more slowly than that due to silica or asbestos.

Pneumoconiosis associated with talc exposure presents a spectrum of natural history ranging from rapidly progressive pulmonary impairment leading to cor pulmonale and death to relatively benign dust deposition producing few symptoms or functional changes and probably not progressing once exposure ceases. Significant exposures to free silica and/or asbestos appear to predispose to the more severe and rapidly progressive forms of the disease while exposure to the pure mineral talc may have little functional significance. No unique complications have been associated with talc pneumoconiosis. Although an increased risk of tuberculosis has been clearly demonstrated in workers exposed to a significant quantity of silica, this has not been unequivocally demonstrated in workers exposed to

talc. Possible carcinogenicity will be discussed in another section.

In general, treatment for pneumoconiosis associated with talc exposure does not differ from that for other pneumoconioses. Efforts to prevent further damage by removal from exposure is certainly indicated when functional impairment can be demonstrated. Treatment of intercurrent infections, bronchospasm, and congestive heart failure by standard means may produce symptomatic improvement but probably do not alter the progress of the pneumoconiosis itself. Two cases have been reported which suggest that the granulomatous reaction may be reversible by the use of steroids.

Diagnostic Criteria

There are no pathognomonic symptoms or signs of the pneumoconiosis associated with talc exposure. As in other pneumoconioses, diagnosis is based upon obtaining a history of significant exposure and finding one of the chest radiographic patterns described above. Although mild functional abnormalities have been described in persons without radiographic abnormalities, this appears to be unusual. In most instances, the radiographic appearance in association with a history of talc exposure should allow a clinical diagnosis to be made with some certainty. In cases where a specific etiologic diagnosis is necessary and the exposure history is inadequate or atypical features are present, lung biopsy can be performed. None of the pathologic patterns described are pathognomonic and particulate matter should be identified by the use of electron microscopy, x-ray diffraction, and lung ashing techniques.

Methods of Prevention

Reduction of exposure, particularly when the talc contains asbestos and/or quartz.

Research Needs

A followup study of workers exposed to nonfibrous talc at least five years after the initial studies would provide information on the incidence of pneumoconiosis, natural history, progression, and provide some estimate of dose-response relationships.

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Montmorillonite Minerals (Smectites)

Montmorillonites are clay minerals. Montmorillonite is the specific name of a clay mineral found originally near Montmorillon, France. The term is now restricted to hydrated aluminum silicates. Bentonite is a commercial term for clays containing montmorillonite type minerals formed by the alteration of volcanic ash. Fuller's earths resembles clay but lacks plasticity and has a higher water and magnesia content. Fuller's earth are commonly magnesium aluminum silicates, but their distinguishing characteristic is their adsorptive qualities; e.g., their ability to decolorize oils and fats by retaining the coloring matter. Attapulgit is quarried as a fuller's earth and has the adsorptive characteristics of fuller's earth.

In most of the studies and case histories reported, the silica and total dust exposures were quite high. Medical findings in these cases were similar to silicosis. In the case of bentonite (and other fuller's earths) the quartz can also be converted to tridymite and cristobalite if high enough drying temperatures are achieved. There is some evidence that montmorillonite itself can cause pneumoconiosis, but its fibrogenic potential is low. If pneumoconiosis occurs as a result of fuller's earth exposure, it is only after long exposure to high concentrations. Disability is slight.

Bentonite

Definition

Silicosis has been reported in bentonite workers. No disease has been associated with bentonite alone.

List of Causative Agents

Definite: Quartz
 Probable: Cristobalite
 Possible: Tuberculosis

List of Occupations and Industries Involved

Bentonite is used as a foundry sand bond; drilling mud where penetrated rocks contain only fresh water; bleaching clay (oil refining, filtering, clarifying, and decolorizing); pelletizing of taconite ore. Minor and specialty uses include: filtering agents (for wine, waste water); water impedance (preventing seepage loss from reservoirs, irrigation ditches, waste disposal ponds, and seepage through basement walls, tunnel walls); ingredient in cosmetics, animal feed, pharmaceuticals; colloidal fillers for certain types of paints; additive to ceramic clays to increase plasticity; fire retarding materials; catalysts for petroleum refining; bleaching oils and making multiple-copy paper requiring no carbon paper.

The major uses of bentonite are in foundry sand (37%), iron ore pelletizing (32%), drilling mud (29%), others (2%).

Epidemiology

Phibbs, Sundin, and Mitchell reviewed the chest films of 32 men who had worked in two bentonite processing plants in Wyoming (2). These films were from the local hospital and physicians and were not a random sample of bentonite workers. An average of 53 men worked at the processing plants in the towns where these films were reviewed. Three physicians—one a radiologist—reviewed the films. Examination of the biased (nonrandom) sample of bentonite workers revealed silicosis in 14 (44%), including 2 cases of progressive massive fibrosis. One of these had worked only 12 years in the mill and was only 40-years-old. Environmental surveys of bentonite processing plants revealed that the free silica content of the airborne dust was between 5-10%, and the airborne dust levels exceeded the TLV for silica; in one plant the dust levels were 3 to 10 times over the TLV. The free silica content of Wyoming bentonite clays ranged from 0-24%, and varied widely in both settled

and airborne dust. This variability conformed with the industry's product information that the chemical composition of the finished product may vary. Tests in the early 1950's showed that some samples contained appreciable amounts of cristobalite but not tridymite. It is not clear whether the cristobalite originated in the parent rock or was formed in the drying process. The dust levels in most cases greatly exceeded the TLV of 20 mppcf for inert dust.

Estimate of Population at Risk and Prevalence of Disease

In 1975 bentonite was produced in 12 states. Almost 3/4 of it was mined in Wyoming. A total of 3,299,267 short tons were sold or used in 1975, a 2% decrease from 1974. The total mining force is probably less than 1,000 workers. The prevalence of silicosis among bentonite workers is unknown, but could possibly be quite high if the result of Phibbs, Sundin, and Mitchell's study is any indication (2).

Pathology—No reports.

Clinical Description

Clinical descriptions of symptoms (dyspnea) and chest x-rays (nodules and fibrosis) are consistent with silicosis. FVC, FEV₁, and MMEF were reduced only in some cases and not others. Progression of the disease was noted in at least 2 cases with severe disability.

Diagnostic Criteria

Same as for silicosis.

Methods of Prevention

Bentonite clay is mined in open pits. In the mill, moisture is removed by kilns or dryers. The dry product is ground in roller mills and the product is then loaded or bagged. The largest exposure is in the bagging and loading operations, although it appears that all mill operations presently get some exposure. Adequate ventilation to remove the dry product is essential to control exposure levels. The federal standard for free silica and cristobalite should be enforced.

Research Needs

An epidemiological morbidity study should be conducted among the miners and millers of bentonite to determine the prevalence of silicosis.

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Fuller's Earth

Definition

The disease is pneumoconiosis, often resembling silicosis. There is no recognized disease specific for fuller's earth.

List of Causative Agents

Definite: Montmorillonite
Probable: Quartz
Possible: ---

List of Occupations and Industries Involved

Fuller's earth is a porous colloidal aluminum silicate. The term is a catch-all for clay or other fine-grained earthy material suitable for use as an adsorbent and bleach. Most uses of fuller's earths refer to its adsorbent properties, although other properties are required for some uses (e.g., drilling muds and fillers). Attapulgus clay (attapulgite, palygorskite) is a crystalline hydrated magnesium aluminum silicate and is the principal member of sorptive clays known collectively as fuller's earth. In the United States, attapulgite is mined only in the Georgia-Florida area. Colloidal grades of attapulgite are used in water-base and oleo-resinous paints as thickening, antisag, and leveling agents, and in latex paints as a thickener. Attapulgite effectively prevents bleeding in putties and glazing compounds, is a thickener for adhesives, and is used in joint-sealing compounds and microcrystalline wax. Oil well drilling mud contains 2-30% clay, and attapulgite is extensively used in salt formations. Attapulgite is used to prevent sedimentation of solids in suspensions and emulsions such as liquid fertilizer suspensions, pesticide dispersions, and emulsions, resin, dispersions, oil-in-water emulsions, graphite dispersions, cosmetic preparations, and portland cement slurries for cementing oil wells. Attapulgite efficiently thickens aqueous and organic liquids such as lubricating oils, alcohols, ketones, ethers, esters, chlorinated aliphatic hydrocarbons, linseed oil,

soybean oil, wax compositions, liquid polyesters, and fire retardants. The binding power of attapulgite is utilized in oil-bonded foundry sands, bauxite granules for sugar refining, molecular sieves, and cosmetic preparations such as rouge and bath powders. In concentrations of 9-10%, modified attapulgite improves compression characteristics and increases the volume of elastometers and polyurethane foams.

Attapulgite has a variety of sorptive uses. It is used to purify oils, fats, waxes, resins, vitamins, brewery products, water, industrial wastes, and sewage by the adsorption of impurities. Attapulgite has been used with success in reclaiming rubber, oils, solvents, fiber from scrap waxed paper and is an excellent adsorbent for radioactive wastes. Allapulgite prevents caking, sticking, and gumming of fertilizers, chemicals, and resins. Attapulgite coatings are used on ammonium nitrate pills for explosives, and conditioning urea with 5-50% attapulgite increases the utilization of urea in animal feeds. The most widely used solid carrier for insecticides, herbicides, and soil fumigants is granular attapulgite. Attapulgite is being developed for use as a filter aid for sugar refining and water treatment. Because of its lack of toxicity and high adsorption, about 10% attapulgite is used in pharmaceuticals, particularly intestinal preparations. In antacid preparations, attapulgite helps control the neutralization rate. Attapulgite is used as an adsorbent for the removal of water, grease, oil, dirt, dust, and odors in factories, farms, canning plants, butcher shops, tanneries, garages, grocery stores, greenhouses, power plants, warehouses, and for litter and bedding for laboratory animals, poultry, and pets. Other sorptive applications include: 5-15% attapulgite in dry-powder fire extinguisher for lithium and other light metals; addition of 5-10% to tobacco to reduce the inhaled tar content; thin coatings as a dielectric capacitor.

Catalytic applications include its use in NCR (no carbon required) paper; in petroleum refining; and chemical processing (polymerization of styrene, depolymerization of isobutylene, carrier in the radiation synthesis of chemicals). The primary uses are for absorbents (65%), pesticides and related products (~15%), oil treatment (~5%), and other (15%).

Epidemiology

There are no epidemiological studies of workers exposed to attapulgite. A mortality

study by NIOSH is currently being analyzed and a morbidity study is planned.

An epidemiological study of workers exposed to fuller's earth was conducted in a plant in Olmstead, Illinois (2). The dominant mineral being mined was the silicate montmorillonite. Other constituents in order of abundance were quartz, muscovite (1-2%), glauconite (1-2%), and amorphous silica ($\leq 1\%$). The amount of quartz in fuller's earth is variable ranging from 0-20% (3)(7). Occasionally albite, sillimanite, staurolite, common hornblende, ilmenite, microcline, kyanite, tourmaline, zircon, rutile, epidote, and leucosene are also found. Five years prior to the medical survey of the workers, impinger samples were collected. Dust counts were as high as 57 mppcf and as low as 2 mppcf. Chest roentgenograms were available on 49 men. The authors concluded fuller's earth can cause a pneumoconiosis similar to silicosis. The prevalence of bronchial markings of fuller's earth workers seen were 1/4 that seen among soft coal miners.

Unfortunately, this study is difficult to interpret. Aside from the difference in numbers between the text and the table, there is no indication of how the x-rays were classified. No information on the comparison group of coal miners was given (e.g., age, years, exposure), so the validity of the comparison is unknown. It is not known whether symptoms (many present only slight clinical findings) were related to exposure and no smoking histories were available. The x-ray findings were highly correlated with age and apparently not related to exposure. It is also possible that other occupational exposures could have produced the observed effects including exposure to quartz as part of inhaling fuller's earth.

Estimation of Population at Risk and Prevalence of Disease

Probably the only significant exposure occurs in mining and milling. The production of fuller's earth was reported in 9 states with Georgia and Florida accounting for 70% of domestic production. Production from Decatur County, Georgia, and Gadsden County, Florida, is predominantly attapulgite, and employs 400-500 workers. Most of the fuller's earth produced in other areas of the United States contains varieties of montmorillonite and comprises 30% of 1975 production. The total population of workers mining and milling about 1,200 short tons is

tons is about 800-1000 workers. The prevalence of disease is unknown.

Pathology

Only four cases of pneumoconiosis from fuller's earth with autopsy have been reported in the literature and all worked in the Nutfield district of Surrey in England (1)(4)(6). The milled product contained 85% montmorillonite and 0.8% quartz. Other constituents were calcite, feldspar, sphene, apatite, barytes, and other miscellaneous minerals. None of these cases showed any evidence of tuberculosis. The main lesions were primarily in the upper lobes and consisted of round, firm (but not hard) black nodules. Aggregations of macrophages were enmeshed in reticular fibers and contained birefringent particles of montmorillonite, the major mineral in fuller's earth. Mild collagenous fibrosis was sometimes present. The fibrosis tended to be reticular rather than nodular. Particle deposition was most common in the bronchioles and air spaces, though a considerable number also reached the lymphoid tissue. The deposition pattern of montmorillonite particles was intermediate to silica and asbestos, presumably because they are larger than silica particles but smaller and shorter than asbestos fibers. Montmorillonite is less irritant and produces less collagenous fibrosis than silica and asbestos. No quartz was noted in these studies. Emphysema was generally present, but no notice was taken of smoking habits. Exposure was not documented except by types of jobs, although it seems reasonable to assume it was quite high. Exposure duration was lengthy; in three cases it was ≥ 35 years; in the fourth case it was unknown. Productive cough and dyspnea were of concern only in the last two years before death (in the two cases where symptoms were noted). There were no data on pulmonary function.

MSHA reported two cases of pneumoconiosis related to the processing of fuller's earth in South Carolina (5). Both worked in the bagging and serving area of the processing plant and were exposed to free silica concentrations considerably in excess of the TLV. Total dust levels over an eight hour shift were also high (6.2-49.6 mg/m³). Respirators had been provided by the company, but they "were not very effective or comfortable," and it was not a company rule that they were to be worn.

The fatal case was a black 40-year-old female who had worked for 5 years, 1 month and had no other dust exposure. The death certificate showed the immediate cause of death as respiratory insufficiency, the underlying cause as pulmonary fibrosis (Hamman-Rich syndrome). The autopsy report listed "extensive pulmonary fibrosis, most likely secondary to silica or mixed dust pneumoconioses and acute *Pseudomonas Aeruginosa* pneumonia."

The other case was a 40-year-old female who after 6 years employment was awarded 100% disability because of a "chronic restrictive condition which indicated pneumoconiosis." She was originally thought to have tuberculosis.

Although descriptions of the medical status of these two workers is limited, the probable causative agent was the extremely high airborne silica exposures. The role of attapulgite and/or hematite is not known, although attapulgite dust levels were also very high during the working lifetime of these two women.

Clinical Description

Middleton describes five cases of men working on the grinding and sieving of fuller's earth (2). The x-rays of 3 men working 4, 5, and 19 years were normal. The man working 35 years had definite changes, and the man with 39 years exposure had "shadows suggesting nodulation with a linear arrangement," and resembled films of hematite iron-ore miners.

McNally and Trostler also describe 6 case histories of the 49 workers they examined in their cross-sectional epidemiological study and a 7th worker not in the study (2). No mention of symptoms in workers with an x-ray less than grade 4 was mentioned, and no pulmonary function was available on any of the workers. In two cases x-ray changes appeared minimal; exposure times were less than four years. Where x-ray changes were grade 1 and 2, findings indicated exposure and dust deposition rather than any disability. Disability occurred after extensive and lengthy exposure as indicated by extensive opacities on the x-ray.

Appropriate laboratory investigations should include spirometry, chest x-ray, and perhaps DL_{CO}.

Treatment is primarily preventive and should include removal from exposure and cessation of smoking.

Diagnostic Criteria

Diagnosis is made on the basis of x-ray changes and a history of exposure. Diagnosis without an occupational history could be confused with other pneumoconioses (e.g., asbestosis, silicosis).

Methods of Prevention

The greatest hazard from fuller's earth appears to be quartz. Exposure to free silica should be kept below the TLV.

Research Needs

There are no epidemiological studies of workers exposed to fuller's earth. The prevalence of silicosis should be estimated in this population.

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Sepiolite

Definition of Disease

Pleural plaques are a common occurrence. The disease may resemble either asbestosis or silicosis.

List of Causative Agents

Possible: Sepiolite; tremolite and anthophyllite asbestos; quartz.

Probable: ---

Definite: ---

List of Occupations and Industries Involved

The principal fuller's earth deposits other than bentonite and attapulgite is that of sepiolite. The only sepiolite mined is in Spain, although economic deposits have been discovered in Nevada. The greatest hazard is from soil in certain regions of Bulgaria. Meerschaum is the compact variety of sepiolite. The only deposits of potential development in the United States are in Arizona and New Mexico. Meerschaum is easily carved and is used in making pipes, cigar and cigarette holders, and a variety of decorative and ornamental items.

Epidemiology

Burilkov and Michailova found the soil from the yard and field of a family with three pleural plaque carriers contained up to 5% sepiolite (2). Anthophyllite and tremolite asbestos were scarce. The authors suggest that sepiolite was probably involved in the formation of endemic pleural plaques.

In 1970 these authors analyzed soil samples from a tobacco growing region with endemic pleural plaques (region A) and compared it with the soil from another area (region B) without "endemic asbestosis" (1). The rocks of region A were mainly shale, marble, and gneiss with the occurrence of serpentinized ultrabasic rocks containing talc and asbestos. Other minerals included quartz, feldspar, mica, hydromicas, and kaolin.

X-ray diffraction analysis of fibrous particulate revealed kaolinite, montmorillonite, anthophyllite, and tremolite. Sepiolite was found in all samples. The soil in region B was mainly sedimentary rock (conglomerates, sandstone, shale, limestone); the minerals were chiefly quartz, mica, and altered feldspars. No fibrous mineral components were found.

Fluorographic examination of 3,325 persons over 6 years of age in this region of Bulgaria revealed 155 (4.9%) cases of "pleural asbestosis" (5). The radiographic findings included discrete minimal calcifications, clearly defined plaques, and extensive calcified areas. Plaques were nearly always found on the diaphragmatic and mediastinal pleura. Symptoms of chronic cough, expectoration, and chest pain were rare; some patients complained of dyspnea and lassitude at work. The prevalence of plaques was less than 1% in the 20-29 year age group, and increased steadily to over 50% in the 70-79 year old group.

The prevalence was slightly lower in females than males, but the rate of increase with age was similar for the two sexes. The results of the physical examination, blood sedimentation rate, leucocyte count, and tuberculin test on the persons with abnormal fluorograms were not reported. Spirometry was apparently not performed. No information was provided on the association of symptoms with radiographic findings, although it may be inferred that disability was slight and that there were few symptoms. Whether sepiolite was the causative agent remains speculative as asbestos was also present in the soil.

Estimate of Population at Risk and Prevalence of Disease

The population at greatest risk are persons in Bulgaria where the soil contains serpentine rock and where the prevalence of pleural plaques is 5% (but over 50% in older age groups). Industrial exposure is to meerschaum. The prevalence of disease is unknown, as well as whether this compact variety of sepiolite is even causing disease. The population exposed to meerschaum is small, and essentially zero in the United States.

Pathology—No reports.

Clinical

Sepiolite, in one case, has been cited as causing "silicatosis" which appeared on the x-ray as diffuse shadowing (4). *In vitro* experiments showed that sepiolite (and palygorskite) increased acid phosphatase, and decreased lactic acid production in rat macrophages to a greater extent than did chrysotile, actinolite, antigorite, and crocidolite. The hemolytic effect was also greater than the asbestos dusts. Intratracheal injection of 40 mg sepiolite killed 3 rats, whereas antigorite had little effect (3). While the relation between cytotoxicity and hemolysis is not known, it does show that in this system sepiolite is even more potent than asbestos.

Diagnostic Criteria

Pleural plaques and calcification, particularly on the diaphragmatic and mediastinal pleura are characteristic. These pleural changes are similar to those seen in asbestosis.

Methods of Prevention

The etiologic agents are in the soil, and so the total population is exposed. Reducing cultivated crops (e.g., tobacco) and growing more cover crops might reduce dust exposure.

Research Needs

Sepiolite is a general product of weathered serpentine rock and cannot be seen under the light microscope. It is important to know whether the serpentine rock mined or quarried in this country contains sepiolite (and asbestos), and if so, whether pleural plaques are occurring as a result.

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Mica Group

Mica

Like the montmorillonites, micas are also based on the structure of pyrophyllite or talc. However, they are different from montmorillonites in that layers of mica cannot be expanded by water (changed) other than by decomposition. There are three important groups of micas: muscovites, lepidolites, and biotites. Muscovite is a wide-spread and common rock-forming mineral and is common in granites, granite pegmatites, metamorphic rocks. Sericite is a variety of muscovite and occurs as fibrous aggregates of minute scales and is usually an alteration product of feldspar. Paragonite occurs with muscovite and is physically indistinguishable from it. Only muscovite and phlogopite are commercially in demand. Lepidolites and biotites have no commercial use.

Definition

Exposure to mica can produce radiographic changes consistent with pneumoconiosis, but the

fibrotic changes may be due to silica and/or asbestos.

List of Causative Agents

Definite: Mica

Probable: Silica

Possible: Asbestos

List of Occupations and Industries Involved

The term "mica" refers to a family of minerals of similar chemical composition and to some extent, physical properties. The predominant minerals are potassium aluminum silicates with variable amount of magnesium, iron, and lithium. The better known members of the mica group include muscovite, phlogopite, biotite, and lepidolite. Only muscovite and phlogopite are used commercially.

Deposits of sheet mica in the United States that can be economically mined are found in pegmatites composed primarily of feldspar, quartz, and mica and often with accessory minerals such as garnet, tourmaline, and beryl. Scrap and flake mica is found in granitic rock known as alaskite and is also recovered as a co-product from the production of clay, feldspar, and spodumene.

Sheet mica has excellent electrical and thermal insulating properties which are the basis for its major uses. Historically, sheet mica was used as a thermal window in stoves and shades for oil lamps, as an insulator for early electrical apparatus such as generators and motors, and for vacuum tubes and capacitors. Mica has been used (and in some cases continues to be used) as a liner for gauge glasses for high pressure steam boilers, in the production of small-size heating equipment, as diaphragms for oxygen-breathing equipment, as quarter-wave plates for optical instruments, and as a base for platinum wire resistance thermometers, stove windows, phonograph diaphragms, and lamp chimneys.

Some scrap mica is made into mica paper for electrical insulation. The remaining scrap and flake mica is ground up and used in oil well drilling mud; as artificial snow and flocking material on Christmas ornaments and display materials; as decorative finishes on concrete, stone, and brick; in the manufacture of roll roofing and shingles; as protective coating on welding electrodes, wire, and cable; as a filler to improve the physical properties of asphalt products, pipeline enamels, mastics, cements, adhesives, texture paints, acoustical plaster, ceiling tile, concrete

block fillers, and wallboard joint cements.

Finer particle size mica is used for lubrication and mold release in the manufacture of rubber products and in the manufacture of paints and plastics. Some talcum powders also contain mica (1).

Of the mica sold or used by U.S. producers, 2% was sheet mica, 53% was scrap and flake mica, and 45% was ground mica.

Epidemiology

Dressen et al. conducted a cross-sectional study of 57 men exposed to mica dust almost completely free from quartz, 31 men and 78 women fabricating sheet mica, and 741 men mining pegmatite and sorting it into its constituents of mica, quartz, and feldspar (3). There were no cases of pneumoconiosis in the 109 men and women fabricating sheet mica. All average dust concentrations were less than 3.2 mppcf. The first and third group were combined "because the relation of silicosis to pegmatite-dust concentrations and the relation of pneumoconiosis to mica-dust concentrations seemed to be much the same, and because mica is a constituent of pegmatite dust."

The probability of finding pneumoconiosis in the 57 mica-exposed men and 741 pegmatite-exposed men working for comparable lengths of time, approximately doubled with each twofold increase in dust concentrations above 10 mppcf. No cases of pneumoconiosis were observed in workers exposed to less than 10 mppcf. The number of years before pneumoconiosis occurred was 15 to 19.9 years when average exposure was 10-14 mppcf, 10 to 14.9 years when average exposure was 25-49 mppcf, and 5 to 9.9 years when average exposure was ≥ 50 mppcf.

The most characteristic x-ray finding in the mica-induced pneumoconiosis was a fine granulation of uneven density that was not readily observed until the usual linear pulmonic markings were more or less obliterated. They were mostly localized in the middle or lower thirds and resembled x-rays of workers in the dry breakers of anthracite mines exposed to dust of low quartz content in concentrations between 200 and 300 mppcf. The markings in the mica-induced pneumoconiosis were qualitatively different from classical silicosis, with a tendency for coalescence of shadows in some cases.

The results of this study indicate that ex-

posure to greater than 10 mppcf of the silicate mica can result in a pneumoconiosis that is distinct from silicosis. Dyspnea, cough, weakness, loss of weight, diaphragmatic fixation, rales, and abnormal breath sounds increased with increasing fibrosis.

Vestal, Winstead, and Joliet, in a cross-sectional study examined 1,121 men employed in the mica industry in western North Carolina (19). Environmental dust counts in grinding and in the underground mines were sometimes as high as 1 billion particles per cubic foot! The population was divided into four groups: (1) a comparison group of 222 with no mining experience; (2) a comparison group of 443 who had worked in mining or mineral grinding of feldspar, iron, copper, asbestos, kaolin, etc., but not mica; (3) 456 men with any exposure to mica—on the average, 54% of their exposure time was to mica and 46% was similar to the second group; (4) a subset of the third group comprising 79 men with no mining experience or silica exposure, who had worked only in mica grinding plants. Mica exposure was presumably quite high. The prevalence of pneumoconiosis in each group was 0%, 5%, 9%, and 11% respectively. The percent pneumoconiosis increased with age and years worked in mining, and the rates were higher in the third group with (any) mica exposure than in the second group with no mica exposure. Whether this was due to the mica, however, cannot be evaluated because the mica group had also worked longer (almost twice as long) in all mining, even though they were the approximate same age. Thus, the mica group had more overall exposure to dusts that could cause pneumoconiosis.

Group 4 (exposed to mica without free silica) appeared to have a higher prevalence of pneumoconiosis than did group 3 (exposed to mica and quartz). A direct comparison cannot be made between these two groups, however, because the age grouping of the "clean mica" group was not available. Results from the fourth group, exposed only to mica, showed that working in plants grinding mica, could result in chest x-ray changes in a relatively short time. The severity of the changes and whether there was associated disability are unknown. Information on symptoms, spirometry, and smoking history were not obtained. Environmental levels were very high (nearly as high as 50 times the recommended standard of 20 mppcf). It is thus not

possible to estimate the hazard of mica at lower exposure levels.

Smith examined 302 men making mica insulators (18). A number of the operations were "dusty," including sawing, sanding, and drumming of the insulators. No pneumoconiosis was observed, but 5 workers (1.6%) had pleural calcification. No exposure data were available.

Heimann et al. examined 329 male mica miners in India (7). The mica in the Bihar mines was in pegmatites that ranged in content from almost pure feldspars to almost pure quartz. Nine random samples of drilling revealed a free silica content ranging from 11% to 67%, with a median of 42%. Minor minerals such as tourmaline, beryl, and garnet were also present. Some mines were dry, others moist; some used dust control and some did not. The mean exposure (mppcf) at different jobs in dry rock ranged from 7 to 1,000 mppcf, and from 5.3 to 600 mppcf in moist rock. There was a decided dose-response effect, with the severity of the x-ray changes increasing with the dose. The dustiest job was that of pneumatic drilling without control. The rate of silicosis among the 177 miners who had never done such drilling was 25%, whereas 44% of the 152 who had done pneumatic drilling without control had nodular or conglomerate silicosis. The rate of nodular or conglomerate silicosis was 40% in those who had worked as drillers for less than 6 years ($n = 51$), 67% in those who had worked 6-10 years ($n = 14$), and 100% in the 2 workers with more than 10 years as a driller. Roentgenographic and clinical data revealed that 18.6% of the miners had pulmonary tuberculosis. These same authors also examined 61 workers who processed only muscovite mica containing less than 1% free silica (7). The exposure of most workers average 10 mppcf (2-21 mppcf range); dust concentrations in the job of sizing mica splittings (sieving) average 40 mppcf (6-130 mppcf range), and the averaged exposure in the job of pulverizing scrap mica into powder mica was 135 mppcf (44-300 mppcf range). Mean exposure for the entire group was 360 mppcf (range = 50-1440). Most of the workers had exposure for less than five years. None had conglomerate silicosis, although 44% had x-ray changes suggestive of an occupational effect.

It would appear from these two studies that mica in the absence (less than 1%) of free silica is not as likely to produce nodular or conglomerate fibrosis on x-ray as mica containing

significant amounts of silica. The accumulated time of exposure was short in the second study, however, and so it is not possible to determine whether nodular or conglomerate fibrosis would develop with higher and/or longer exposure to mica in the absence of free silica. It does appear that relatively short exposure times can produce x-ray changes. There is no indication in either paper about disability, pulmonary function, symptoms, or smoking.

Mica can cause pneumoconiosis in exposed workers. In some cases the latency is short, i.e., within five years. The epidemiological studies have been confined to x-ray changes, so there are very few data on the relation of x-ray changes to symptoms and pulmonary function. Even the x-ray changes have been poorly described, and cannot be compared to present-day classification systems. There is no information on smoking in any of the studies. Quartz and other silicates are commonly associated with mica exposure for the miner. Thus, other exposures to fibrogenic minerals confound the analysis of dose-response relations. This is less true in processing where the exposure is to relatively pure mica. The interaction of tuberculosis and mica in producing fibrosis is not known, but tuberculosis does not seem to be as important as it is for silicosis.

Sericite

In 1933 Jones attempted to show that sericite, a variety of muscovite mica, was the cause of silicosis. Muscovite occurs as platy crystals and scales, whereas sericite occurs as minute scales and as fibrous aggregates.

Hurlbut and Beyer compared the silica and sericite content in dust from two foundries located in the same town (8). Foundry A had had more than a score of deaths due to silicosis and silico-tuberculosis. Foundry B had no silicosis claims over the same period. The characteristics of the two foundries were similar except that foundry A used fine "facing" sand that was not used by foundry B. One of these facing sands made up 7% of the molding sand and over 75% of the total number of particulates in this sand were sericite; all of it was of respirable size. This study supports the conclusions of Jones (9). Unfortunately no data on x-ray findings were given.

Several animal and *in vitro* studies support the view that sericite cause fibrosis. Drinker, Field, and Drinker observed changes in lymph

nodes injected with sericite that were similar to the changes produced by silica (4). Policard observed that phagocytes exposed to mica dust behaved like phagocytes exposed to dusts of rock containing quartz and various silicates (including sericite) (16). In both studies needle-like mica particles were seen in the plaques. Cummins observed similar changes (2).

Intratracheal injections of ground-up sericite in animals did not produce a fibrotic response resembling that produced by quartz (5)(12). No pictures were provided, but the fibrous nature of the sericite may have been destroyed. King, Gilchrist, and Rae showed that if the sericite or mica were pre-treated with sodium chloride, it would produce a fibrotic reaction when injected into the trachea of white rats, but would not do so when untreated (10).

Despite the prevailing dogma that free silica is the causative agent in silicosis, Jones' theory deserved further investigation. The negative findings in several animal studies (all intratracheal injection) of ground-up sericite are not sufficient reasons to drop Jones' idea, particularly in the face of positive data on human subjects.

Estimate of Population at Risk

MSHA estimates that in 1978 there were 72 open pit miners, 267 workers in preparation plants, and 43 office workers, or a grand total of 382 workers involved in the mining and processing of mica. The number exposed may be larger, however, as sheet mica (from North Carolina) was not mined as the primary product. Scrap and flake mica were produced from the beneficiation of pegmatite ores, clay deposits, and weathered pegmatite and schist areas. The prevalence of disease among current workers is not known.

Pathology and Clinical Description

Middleton described a study by Ferguson of 12 workers exposed to mica dust (13). Five of the 12 had worked for more than 5 years, and 4 of the 5 had slight symptoms of cough and dyspnea. The fifth man had more severe cough and dyspnea, "well-marked" pulmonary fibrosis, and emphysema. Another man employed 8 years had "quite definite fibrosis." Chest x-rays of 2 of the 5 men revealed "increased hilum shadows with increased linear striation and fine diffuse shadows in the middle zones." The chest x-ray of another man employed 32 years

"showed fibrosis, largely peribronchial in type, chiefly in the middle zones, with increased hilum shadows, and at one or two points, nodule formation." Ferguson tentatively concluded that mica dust may be capable of causing pulmonary fibrosis. No information was given as to exposures other than mica.

Dreessen et al. described two cases of pneumoconiosis due to mica (3). One was a 55-year-old white male who had worked for 24 years in a mica grinding plant with a weighted average dust exposure of 50 mppcf. He had had slight dyspnea the year prior to examination. Breath sounds were diminished over all portions of the chest and there was slight restriction of diaphragmatic movement. The x-ray revealed diffuse ground-glass appearance, most pronounced at the bases, and obliteration of the left costophrenic sulcus. The other case was a 51-year-old white male who had worked in a mica mill for 10 years and a mica mine for 10 years. His estimated weighted dust exposure was 20 mppcf; he had some quartz and pegmatite exposure as a miner. He had no symptoms. His x-ray showed second-degree diffuse granular appearance, shallow left costophrenic angle, and pleural thickening in the extreme left apex.

Vorwald described a case of "chronic proliferative pneumonitis" in a rubber worker who was exposed to dusting powder (20). After about 30 years, he developed progressive shortness of breath and a bilateral "pronounced diffuse increase in linear markings, particularly in the lower portions of the upper lobes." Autopsy revealed diffuse, widespread pigmented fibrosis, emphysema, and some "irregular massive lesions." Tracheobronchial lymph nodes were mildly pigmented, small, and soft. The pigmented crystals were mainly biotite mica; some could have been talc. No free silica was found. Whether the mica caused the fibrosis would not be determined because of the probability of other fibrogenic agents in the occupational environment.

Kleinfeld described two cases of silicosis in individuals exposed to muscovite mica. One had symptoms, reduced lung function, and an x-ray abnormality while the other did not. Both had pleural calcification (11).

Pimentel and Menezes reported a case of a 46-year-old woman who for 7 years was exposed to mica dust during grinding and packaging operations (15). Dyspnea on exertion, pro-

gressive weakness, and loss of weight appeared after a "common cold" and five years exposure. After 7 years exposure, physical examination revealed fine crackles in both lungs and an enlarged liver. The chest radiograph showed some nodular densities in the LLL and bilateral reticulomicro-nodular shadows. Diffusion capacity and FVC were reduced, and there was hypoxemia and hypocapnia. Three years later the patient died in respiratory failure. On autopsy the lung showed extensive areas of diffuse fibrosis, emphysematous foci, and honeycombing with a proliferation of histiocytes and fibroblasts and the formation of reticular and collagen fibers. Within the thickened interalveolar septa of the lung were identified plate-like crystals of muscovite mica; dark brown or black material in the lesions were not identified. Sarcoid-like granulomas in the liver also contained crystals (mica) and dark brown inclusions. There was no history of exposure to other dusts or other respiratory diseases, and no other contaminants were found.

The findings in mica pneumoconiosis are similar to other pneumoconioses; i.e., restriction and shortness of breath, and reduced diffusion. X-ray findings are of a diffuse fibrogenic pneumoconiosis.

Appropriate laboratory investigations should include spirometry and chest x-ray.

Diagnostic Criteria

Criteria for diagnosis should include: history of exposure of ≥ 5 years; chest x-ray with reticular nodular shadows; restriction and reduced diffusion.

The disease may be confused with sarcoidosis.

Methods of Prevention

Reduce exposure.

Research Needs

The prevalence of disease among present-day workers is unknown and should be determined.

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Hydrous Micras and Illites

These are micras of secondary origin. They contain silicates of potassium, aluminum, iron, and magnesium with water. The terminology of the group is not well established, being variously called illites, hydromicra, hydrous micras, hydromuscovite, and hydrated micras. These minerals are the predominant alkali-bearing constituents of many sedimentary clays, shales, and fireclays. The illites are secondary minerals, which commonly occur in clays; they are not mined as minerals.

Vermiculites

Vermiculites are ferromagnesium aluminum silicates that exfoliate to a low density material when heated. In its natural state vermiculite resembles mica in that it splits readily into thin, flexible, but inelastic laminae. The space between layers can be penetrated by electrostatically neutral molecules, such as water. When heated rapidly, the water between the layers turns to steam, and the vermiculite expands into worm-like pieces. The increase in bulk volume is 8-12 times.

Definition

No described disease entity. If disease does occur, it would be pneumoconiosis.

List of Causative Agents

Definite: ---

Probable: ---
Possible: Asbestos

List of Occupations and Industries Involved

Vermiculites have no exact formula or composition but are families of related minerals, mainly hydrated magnesium silicates. The term vermiculite has been applied to the columnar, bloated products of calcined and bleached phlogopite. Most of the uses of vermiculite are for the expanded form, and 80% of this is in construction (loose fill insulation, treated granules for insulation of masonry walls, lightweight aggregates combined with setting materials such as gypsum, asbestos, portland cement, acoustical plaster formulations, components in rigid board or tile products). Nonconstruction uses include a carrier for fertilizers and agricultural chemicals, soil conditioner; industrial uses include cryogenic insulation, insulation of appliances, coolers, safes, insulating component in prefabricated chimneys, oil-less lubricant, aggregate in refractory components, slow cooling of steel, cushioning material in packaging applications, insulation of underground steam or hot water lines, window display material, grease or oil absorbent, sound-deadening applications, nuclear waste disposal, and animal litter. Vermiculite is particularly important as a potential substitute for asbestos.

Epidemiology

Brooks and Lockey, in a preliminary report of workers exposed to vermiculite containing tremolite-actinolite asbestos, identified benign pleural effusion and possibly a high prevalence rate of pleural and parenchymal lung disease. They suggest the adverse health effects are a result of the asbestos contamination rather than the vermiculite itself. There are 2 animal studies that report effects of vermiculite. Hunter and Thomson exfoliated and ground South African vermiculite so that the majority (97%) of the particles were less than 20 μ (3). Twenty-five mg of vermiculite were injected into the pleura of 50 rats. There was no disturbance of growth rate or survival over the 104 days of the study. The rats injected with vermiculite were similar to the control saline injected rats except for the presence of pleural adhesions and abscesses which were observed in rats injected with vermiculite. This was attributed to accidental infection during the injection and exacerbated by the presence of the foreign material. No lung tumors

were observed in either the control or vermiculite injected rats.

Goldstein and Rendall injected rat tracheae with South African vermiculite containing 1.4% quartz and serpentine, apatite, calcite, and magnetite as minor constituents. (Dose was 600 sq cm/ML and 50 mg/ML) (2). Four months later, the degree of fibrosis was evaluated on a scale of 0-4, where 4 was a relatively acellular collagenous fibrosis produced by quartz. In grade 1 fibrosis the lesions were cellular, with some loose reticulin but no collagen. The vermiculite exposures produced a grade of from 0 to 1.

Thus, on the basis of animal studies, the vermiculite does not appear to produce tumors (as did asbestos) or fibrosis (as did quartz).

Estimate of Population at Risk and Prevalence of Disease

There are 2 major producing deposits in the United States. The Montana deposits contain biotite, several amphiboles near hornblende in composition, and apatite in some areas. The South Carolina deposit contains the accessory minerals feldspar, actinolite, tremolite, hornblende, and quartz with minor amounts of apatite, zircon, magnetite, and talc. Some vermiculite contains significant proportions of fibrous tremolite and chrysotile (1). Three-hundred sixty-five thousand tons were produced in the United States in 1973. In 1978, an estimated 101 open pit miners, 215 workers in preparation plants, and 66 office workers were employed in the vermiculite industry. The occurrence and prevalence of disease are unknown. An oral communication without details or documentation reports a prevalence of 20% abnormal x-rays in an asbestos-contaminated vermiculite mine in Montana.

Pathology — No reports.

Clinical Description — No reports.

Diagnostic Criteria

The criteria for pneumoconiosis should be used on chest x-ray and spirometry. The presence of asbestos and/or quartz as contaminants could produce a disease similar to asbestosis and silicosis.

Methods of Prevention

Keep exposure to silica and asbestos below standards.

Research Needs

There are no studies on the effect of either expanded or nonexpanded vermiculite in human populations. A prevalence study should be conducted in populations exposed to both types of vermiculites, particularly in light of the potential for increased use as an asbestos substitute.

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FRAMEWORK STRUCTURES

This group is important because nearly $\frac{3}{4}$ of the rocky crust of the earth is composed of these minerals, which are stable and strongly bonded.

Silica Minerals (SiO₂)

The silicon dioxide group of silica has the simplest structure, but even in this group there are at least 9 different possible structural arrangements and, therefore, 9 different polymorphs. Quartz, tridymite, and cristobalite are the three principal crystalline polymorphs of silicon dioxide and can be transformed from one to the other under different conditions of temperature and pressure.

Cryptocrystalline varieties may be divided into fibrous and granular. A general term for the fibrous varieties is chalcedony; the varieties of chalcedony include carnelian, chrysoprase, agate, onyx, heliotrope. Granular varieties include flint, chert, and jasper. All of these

varieties can contribute to the "free silica" rock. If silicon dioxide is part of the structure of a silicate, it is not free silica but is known as combined silica. The fibrogenic potential of free silica is considerably greater than that of combined silica. When the chemical analysis of a rock gives "total silicon dioxide," the contribution of free and combined silica is not known. Free silica will be discussed later.

Quartz, when present as a contaminant (greater than 1%) with other inorganic dusts, may increase the effect of the associated dust, at least for coal and iron ore (2). The presence of other cations in the quartz structure (e.g., aluminum, iron) reduces the biological activity of quartz (2). The relation of quartz to other silicates and their fibrogenic potential should be investigated.

Minerals Isostructural with Silica Minerals

Nephelite is a mineral structurally similar to tridymite. Nephelite is used extensively in the ceramic industry as a substitute for feldspar. It is a by-product of apatite mining in Russia where it is also used in leather, textile, wood, rubber, and oil industries. It is the commonest of the feldspathoid minerals and will be discussed there.

Feldspars

Feldspars are the most important of the mineral groups as they are the most abundant minerals of igneous rocks. There are two major groups of feldspars: (1) the potassium feldspars based on orthoclase, and (2) sodium-calcium feldspars (plagioclase group) which form a series from albite and anorthite. The common feldspars are solid solutions of these three components.

Granite is a granular igneous rock containing quartz, much feldspar, and most of the time, smaller amounts of mica (biotite and muscovite), hornblende, and pyroxene. The complete series ranges from granite (feldspar, almost entirely potash varieties) to granodiorite (feldspar, mostly plagioclase). The boundary is arbitrarily set such that granites contain more potash feldspar than plagioclase, and the reverse is true for granodiorites. The quartz content averages greater than 25% and presents the greatest risk to health. Since silicosis is the health hazard from granite, it is discussed in the chapter on silicosis.

Feldspathoids are chemically like feldspars in that they are aluminosilicates of sodium,

potassium, and calcium. However, they contain two-thirds less silica than the corresponding feldspar. The most common feldspathoids are leucite and nepheline. Leucite is a natural potassium-aluminum silicate found in certain recent lavas but never in rocks containing quartz. Although not presently mined, it is a possible source of potash.

Nepheline (nephelite) contains microcline, orthoclase, albite, feldspars, nepheline, and ferromagnesium minerals (principally hornblende, pyroxene, biotite). Commercial deposits contain at least 20% nepheline, 60% feldspar, and usually less than 5% accessory minerals. The most common accessory minerals are magnetite, ilmenite, calcite, garnet, zircon, and corundum. Quartz is not present.

Feldspar

Definition

No described disease. If present, it would be pneumoconiosis, and because of the free silica content, would resemble silicosis.

Causative Agents

Definite: Free Silica

Probable: --

Possible: Feldspar may neutralize effect of quartz.

List of Occupations and Industries Involved

Feldspar (or "spar") is composed of three silicate minerals: microcline or orthoclase, albite, and anorthite. Feldspar is used as a flux and a source of alumina in the manufacture of glass, porcelain enamel, and ceramic products (pottery, plumbing fixtures, electrical porcelain, ceramic tile, dinnerware, art pottery). Finely ground feldspar can be used as a filler in latex, paint, methane, and acrylics. About 65% is used in the glass industry, 30% in ceramics and 5% in fillers and other applications.

Feldspar is obtained primarily from granite and pegmatitic rock, with quartz and mica being the other principal constituents. Other accessory minerals include sand, beryl, spodumene.

Epidemiology—No studies

Estimate of Population at Risk and Prevalence of Disease

In 1978 there were 5 underground feldspar mines, 75 open pit miners, 250 workers in prep-

aration plants, and 41 office workers for an estimated grand total of 371 workers employed in mining and processing feldspar. The prevalence of disease is unknown.

Pathology

Rotter and Gartner described a case of a worker with extensive tuberculosis exposed to feldspar containing 38% to 45% quartz with many of the particles being less than 5 μm (6). Nodules were like those found in silicosis but were more widely disseminated. There was less collagenous tissue and reticular fibers than in silicosis. They hypothesized that aluminum, potassium, sodium, and calcium ions had leaked into solution and exerted a neutralizing effect on the quartz.

Animal experiments (intratracheal and intraperitoneal) showed that feldspar produced a less fibrogenic reaction than did quartz (1)(4)(7).

Meiter and Toering and Nagelschmidt observed that feldspar may act like quartz because alkali feldspar has a crystal structure similar to quartz (3)(5).

There is very little published information on the effects of feldspar in humans. Animal experiments show little fibrogenic activity from feldspar. Quartz is always associated with feldspar exposure, and the risk is from quartz, with feldspar perhaps providing a diluting or neutralizing effect.

Clinical Description—No reports.

Diagnostic Criteria

If disease occurs, it is similar to silicosis.

Methods of Prevention

Keep silica exposure below the standard.

Research Needs

The prevalence of disease among feldspar miners and millers is unknown and should be determined.

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Nepheline

Definition

No recognized disease entity.

List of Causative Agents

Definite: ---

Probable: ---

Possible: Feldspar, mica

List of Occupations and Industries Involved

Nepheline syenite is a crystalline rock consisting of the feldspars albite and microcline; it contains no free silica. The principal ferromagnesium minerals present are hornblende, pyroxene, and biotite. The most common accessory minerals (usually less than 5%) are magnetite, ilmenite, calcite, garnet, zircon, and corundum. Nepheline syenite is used in the manufacture of glass products (container glass, fiber-glass, opal glass, plate glass, sheet glass, tableware glass), whiteware (dinnerware, sanitary ware, floor and wall tile, electrical, chemical and dental porcelain, art pottery, porcelain balls, mill liners), extender pigment and fillers (interior and exterior latex and alkyd paints, traffic paints, metal primers, exterior wood stains, sealers, undercoats, hardboard ground coats, PVC, epoxy and polyester resins systems, foam carpet backing). In the USSR, it is also used to manufacture alumina for aluminum, sodium and potassium carbonates, and portland cement. There are two mines in the United States (in Arkansas), and the rock from these mines is used only for construction aggregate and roofing granules.

Epidemiology—No studies

Estimate of Population at Risk and Prevalence of Disease

As there are only two operating mines in the United States, the mining population is quite small. Nepheline used for other purposes is imported primarily from Canada. The prevalence of disease is unknown.

Pathology and Clinical Description

Barrie and Gosselin reported a case history of a man exposed to massive quantities of Canadian nepheline rock (1). He worked for four years at a mill where hematite was removed from finely powdered nepheline. The dust was dry and exposure was "extremely high." In his fourth year of work he noticed increased dyspnea. Two years later he was found to be easily cyanosed on exercise and to have increased peribronchial markings on x-ray. Pulmonary function (ventilation, lung volume, gas mixing) were within normal limits, and there was a moderately severe reduction in diffusion. The effects of exposure were complicated by a duodenal ulcer existing prior to exposure, and Cushing's Syndrome that began while exposed to nepheline dust. Four years after cessation of exposure he had three bouts of pneumonia. He was believed to have died of respiratory failure. Deposition and associated pathological changes in the lungs were related to the amount of dust accumulation in the lung. In a small portion of each lung there was slight deposition with dust in phagocytes, normal alveolar walls and bronchi, diffuse emphysema, and no collagen but an intercellular net of argyrophil fibers. Where there was abundant dust accumulation encircling the mouths of alveolar ducts, atria, and alveolar sacs, there were occasional collagen fibers and a more pronounced argyrophil network, manifested by progressive involvement of the smallest and some of the larger pulmonary arteries by the argyrophil net, fibrous thickening of intima, and pigment penetration of vessel walls. Where there was massive dust accumulation, the pathological changes were similar, with the addition of intra-alveolar exudates of fibrin and branching plugs of connective tissue extending as far as the respiratory bronchioles. The plugs contained dust which was both in and out of macrophages, and there were many coniphages mixed with fibrinous exudate. In addition, small pulmonary arteries were frequently occluded and there was some focal

necrosis and cavitation. Small particles and acicular crystals were both observed. The authors suggested that the fibrosis and massive pneumoconiosis were caused by the acicular crystals. The massive pneumoconiosis differed from anthrosilicosis and fuller's earth pneumoconiosis in that the area of consolidation was white, and lesions were in the lower lobes.

Because there is probably no milling of nepheline in this country, there are unlikely to be exposures of the same magnitude. The authors commented on the relatively small amount of fibrosis, which may have been related to the cortisone treatment for Cushing's Syndrome. The disturbances in both function and structure of the lung were quite small considering the amount of dust deposition. Thus nepheline would appear to present little hazard at low dust levels.

Diagnostic Criteria

The criteria for diagnosis should be the same as for pneumoconiosis.

Methods of Prevention

Hazard appears to be low. Disease will be prevented if exposures are not excessive, but the standard should probably be less than for nuisance dust.

Research Needs

There is little data on the hazard for nepheline. In the United States, the number of people with high exposure is not large, and exposure among secondary users is probably not significant.

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Zeolites

The zeolites are a large group of hydrous silicates with aluminum, sodium, and calcium as important bases. The gross composition of zeolites resembles that of feldspars. Zeolites have the important (commercial) property of reversible selective adsorption. Today, any aluminosilicate with this property is referred to as a zeolite, as well as clay minerals and synthetic organic ion exchange resins.

Synthetic zeolites have many advantages over natural zeolites for use as molecular sieve adsorbents and exchange and catalytic processes; they have been produced commercially since the early 1950's. In this country natural zeolites have had only limited use.

Definition

Pleural thickening and calcification and pleural mesotheliomas are associated with persons living in regions where the soil contains erionite zeolites.

List of Causative Agents

Definite: ---
Probable: Erionite
Possible: Asbestos

List of Occupations and Industries Involved

Zeolites are crystalline, hydrated aluminosilicates of sodium, potassium, magnesium, calcium, strontium, and barium. Natural zeolite can occur as a fibrous or nonfibrous form; fibrous forms include erionite and mordenite. Ferrierite and phillipsite are sometimes fibrous. Present and potential uses include the following: drying cracked gas, ethylene, butadiene, ethanol, natural gas; liquid paraffins, and solvents; CO₂ removal from natural gas; n-paraffin recovery from naphtha and kerosene; aromatic separation; dimension stone; pozzolanic cements and concrete; lightweight aggregate; filler in paper; concentration and isolation of radioactive wastes; extraction of ammonia from sewage and agricultural effluents; enhance nitrification in activated sludge processes (sewage treatment); production of high-purity oxygen for secondary-smelting operations, river and pond aeration; pollution control in paper and pulp industries; dietary supplements for swine and poultry; neutralization of acidic soils; agglutinating agents for mixed fertilizers; carriers for fungicides and pesticides; removal of SO₂ and other pollutants from stock gases of oil and coal-burning power plants; sorbent in oil-spill cleanups; purification of natural gas; heat exchangers in solar radiation for air conditioning and water heating; control of moisture content of animal manure odor; soil conditioner; polishing agent in fluoride-containing toothpaste; drying HCl, chlorine, reformer hydrogen, petroleum solvents; catalyst on catalyst carriers in reactions (such as hydrocracking, hydroisomerization, alkylation, and

reforming in the petroleum industry); methane recovery for synthetic fuel production.

Epidemiology

Boris et al. investigated pleural mesotheliomas and chronic fibrosing pleurisy together with the environmental conditions in the small village of Karain, Turkey (3). There were no deposits of asbestos in the area and volcanic rock samples contained calcite, feldspar, quartz, volcanic glass, biotite, chlorite, muscovite, and augite. A more recent report described finding respirable fibers (5-70 μm long) or erionite type zeolite in rock samples, street and field soil, and water (1). The erionite fibers were apparently found only in Karain and not in the neighboring villages 4 and 7 km away. The volcanic rock is used as a building stone, making stucco to plaster the walls, for clearing wine, and making sweetmeat. In the summer, most of the villagers help grow potatoes and onions and are exposed to the dust from the area between the river and the village, as well as dust from the road, which is unpaved. Over the period 1970-1974, 24 of 55 deaths (44%) were due to pleural mesothelioma, and in 62% of the cases, the cause of death was due to malignancy. In 1974 neighboring villages with about 11 times the population of Karain had no deaths due to pleural mesothelioma compared to 11 for Karain. In 1975-1976 there were 16 cases of pleural disease in 8 men and 8 women with ages ranging from 27-65 years. All had chest pain and breathlessness.

In Tuzkoy, Turkey, 312/1126 of the persons over 25 years of age were randomly selected and given chest x-rays (2). The prevalence of abnormalities were as follows: 16% calcified pleural plaques, 10.5% pleural thickening, and 12.5% fibrosis. Of those with pleural thickening, two were later diagnosed as malignant pleural mesothelioma and one as chronic fibrous pleuritis. Erionite type zeolite fibers of respirable size were found in the rock samples, street and field soils of Tuzkoy, but not in the village of Kizilkoy, 5 km away. None of the chest abnormalities seen on x-rays in Tuzkoy were found in Kizilkoy.

Surveys of many villages in several regions of Turkey have revealed a prevalence of calcified pleural plaques ranging from zero to as high as 14% (2)(6). There were also some cases of chronic fibrosing pleuritis and malignant pleural mesothelioma. Some villagers with pleural disease

lived in villages which had asbestos deposits; some did not. The asbestos observed in the stucco was mainly tremolite (and chrysotile, actinolite, and anthophyllite in some areas); in other areas, mica, talc, limestone, kaolin, and other silicaceous minerals were also found along with tremolite asbestos.

Yazicioglu attributed the calcified plaques to chrysotile asbestos (7). Boris et al. originally thought asbestos was causing the mesotheliomas in Karain and elsewhere, despite the absence of asbestos in the rocks, soil, and water (and tissue) (1)(3). Boris, Artuninli, and Sahin now argue that both the mesotheliomas and calcified plaques may be caused by the fibrous zeolite, erionite (2). This thesis is based on the presence of erionite in at least some of the areas where the pleural changes are endemic, and where asbestos may or may not be present. Environmental factors (albeit unknown) other than asbestos have been associated with a high prevalence of pleural plaques (5). Thus, finding pleural plaques is not necessarily a sign of asbestos exposure.

There is little doubt that there is an endemic of pleural findings and, of particular concern, of mesothelioma in two villages in Turkey. The actual prevalence and incidence may differ from the percentages presented since the methods for calculating rates appear subject to bias (in some cases they are not random selections; in others it is not clear how the surveys were conducted). The more important deficiency in these studies involves assessment of exposure. There are no quantitative estimates of the presence of zeolite, asbestos, and other minerals in the air, soil, and water, although samples have apparently been analyzed for these minerals in some areas. To determine the etiology of these pleural changes, a comprehensive evaluation of the environment where the medical surveys are being conducted is needed.

While the studies in Turkey have not "proven" fibrous zeolites may be carcinogenic and have an effect on the pleura similar to asbestos, they provide plausible evidence. Erionite zeolites are needles 10-20 μm in length and 0.5-1 μ wide; mordenite needles are 5-20 μm long and 0.5-1 μm wide (4). The physical properties of fibrous zeolites and asbestos are similar, and all are silicates. Whether the biological activity is similar needs further study.

Estimate of Population at Risk and Prevalence of Disease

The use of natural zeolites is limited at present. Mining and milling occurs on an intermittent basis. The number of potentially exposed workers using zeolite is small because it is packaged, transported, handled, and used in enclosed systems to avoid contact with contaminants that would destroy its properties. The prevalence of disease is unknown.

Pathology and Clinical Description

Boris reported on 120 cases of malignant-pleural mesothelioma (108), asbestos pleurisy (9), and benign pleural mesothelioma (3)(1). Two of the 120 had had occupational exposure to asbestos (automobile industry, construction worker). All the rest were farmers; 52 had used the soil (containing the zeolite erionite) as stucco, food (in their sweets), and for toilet needs as children. Sixteen patients had come from districts in Turkey with asbestos in the soil. The other 50 had no "known chance to inhale asbestotic material," although analysis of the soil from several of the districts revealed the presence of tremolite asbestos along with "considerable amounts of other silicates such as mica, talc, feldspar, and kaolin." In this article, asbestos was assumed to be the causative agent, but subsequent analysis of (at that time) unidentified asbestiform fibers led the author to suggest erionite was the causative agent (2).

The main symptoms associated with malignant pleural mesothelioma and "asbestos pleurisy" were chest pain and dyspnea. Physical and radiological examination revealed pleural thickening or effusion, and four of the cases with mesothelioma also had pleural calcifications. At the time of diagnosis, the average age of the 72 males was 43 years (15-71); for the 48 females, 51 years (12-69). Boris felt that both pleural plaques and asbestos pleurisy might be precursors of pleural mesothelioma, although the number of cases where both were present was small. He also found it difficult to distinguish between asbestos pleurisy and malignant pleural mesothelioma, even after examination of tissue with the electron microscope.

Thoracotomy, radiology, thoracoscopy, and needle biopsy were diagnostic procedures for "asbestos pleurisy" and mesothelioma. Cytologic examination of pleural fluids and sputum, protein level of pleural fluid, and erythrocyte

sedimentation rate (ESR) were also utilized in some of the patients. None of these diagnostic tests were clearly preferable. The importance of showing asbestos fibers in the tissue by EM examination was stressed. Apparently only 5 of the 120 cases had pleural tissue examined, and only one of the five had asbestos fibers (amphibole, chrysotile, talc, feldspar, quartz, mica, and kaolinite) in the pleura.

Progression was variable. Cases of pleurisy and calcification did not progress in some cases; in others they developed into benign mesothelioma or fatal malignant mesothelioma. In the population in Turkey where exposure begins at birth, the pleural changes may be observed quite early (in the teens) although most cases involved older people. Both sexes are affected. An appropriate screening test is the chest x-ray; diagnosis includes a biopsy. Symptoms of chest pain and dyspnea occur, although it is not clear whether symptoms are an early sign.

Malignant mesothelioma is invariably fatal; the prognosis for pleurisy, calcified plaques, and pleural thickening may be quite good—assuming they do not progress to malignant mesothelioma.

Diagnostic Criteria

Pleural changes (thickening, calcification, mesothelioma) are the most characteristic feature of nonoccupation exposure in Europe. These changes are nonspecific and are identified with those caused by asbestos.

Methods of Prevention

There is no known medical problem of industrial exposure in this country. The high prevalence of mesothelioma due to community exposure points to a potential hazard from at least one variety of zeolite.

Research Needs

Better characterization of the dose and the zeolite and asbestos content of the soil in Europe is necessary.

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ASBESTOSIS

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INTRODUCTION

Occupational exposure to asbestos minerals constitutes a major health hazard in the United States and in most industrialized nations of the world. Because of their unique properties such as resistance to heat and chemical attack, asbestos minerals have long been used by man. Finish potters are known to have used soils containing anthophyllite asbestos dating from 2500 B.C. (103). Use of asbestos in lamp wick was described by Theophrastus, Strabo, and Plutarch. Herodotus (456 B.C.) described cremation clothes made of woven asbestos. Marco Polo described tablecloths of asbestos seen during his journeys (66).

Despite early uses, large scale use of asbestos came with industrialization and particularly the steam engine which required heat resistant materials for packings and seals. The first asbestos textile mill in the United States began production in about 1896. Today, commercial uses of asbestos are countless and nearly every manufacturing sector may be involved with production or use of asbestos-containing products.

The term "asbestos" is applied to a group of naturally occurring fibrous silicate minerals. Although many minerals are fibrous in nature, only six are regulated by Occupational Safety and Health Administration (OSHA) standards. These minerals fall into two major mineralogical subdivisions: chrysotile, which belongs to the serpentines; and the amphiboles, including crocidolite, asbestiform actinolite, asbestiform tremolite, amosite, and anthophyllite. Only amosite, chrysotile, and crocidolite are of economic importance. Chrysotile is basically a sheet silicate mineral rolled into itself to form a hollow tube. This tube constitutes the basic fibril of chrysotile.

All amphibole asbestos types are similar in crystal structure: they consist of double chains of linked silicon oxygen tetrahedra between which metallic ions are sandwiched (128). Chemical composition and trace metal contamination (Cr, Co, Mn, Ni associated with chrysotile) of asbestos fibers may vary considerably between deposits from different mining regions (43).

More than 90% of all asbestos used in the United States is of the chrysotile variety. Total U.S. consumption of asbestos in 1977 was 610,000 metric tons, down from peak consumption of 795,000 metric tons in 1973 (12). By contrast, only 93,000 metric tons were produced in U.S. mines and mills; Canada furnished 95% of all imported raw asbestos fiber. U.S. asbestos consumption by end use for 1978 is shown in Table II-9. Asbestos cement products constitute the major use of asbestos followed closely by floor products or materials used in the construction industry. Materials containing asbestos have been extensively used in construction and shipbuilding for purposes of fireproofing and for decoration. These have often been applied by spray application.

DEFINITION

Asbestosis is the name of the pneumoconiosis produced by the inhalation of asbestos fibers. It is characterized by diffuse interstitial fibrosis of the lung parenchyma, often accompanied by thickening of the visceral pleura and sometimes calcification of the pleura. Clinical findings include dyspnea on exertion, non-productive cough, rales at the lung bases, bronchi, and in advanced cases, finger clubbing. Lung function measurements usually demonstrate a restrictive impairment with reduced diffusing capacity.

Table II-9

U.S. ESTIMATED ASBESTOS CONSUMPTION IN 1978 BY END USE CATEGORY

Product	Consumption (Metric Tons)			
	Chrysotile	Crocidolite	Amosite	Anthophyllite
Asbestos cement pipe	119,800	23,300	2,700	
Asbestos cement sheet	28,400		800	
Flooring products	122,400			
Roofing products	58,200	100		
Packing and Gaskets	23,200	100		
Thermal insulation	14,300			
Electrical insulation	3,200			
Friction products	81,000			600
Coating and compounds	29,100			
Plastics	5,300	500		
Textiles	5,700			
Paper	28,400	700		
Other	33,100			2,100
Total	552,100	24,700	3,500	2,700

Source: (12)

CAUSATIVE AGENTS

Asbestosis is perhaps the most widely studied of the known occupational hazards; however, its mechanisms are still not fully understood. Both clinical and epidemiological data have conclusively shown that asbestos is associated with asbestosis and respiratory cancer in man. Animal bioassay data fully support these findings and suggest that pathological responses to asbestos may be more related to physical characteristics of the fibers than to chemical composition. Animal data have shown a wide variety of fibrous minerals and small diameter glass fibers to be capable of producing tumors upon pleural injection or implantation (110)(111)(139). Interstitial fibrosis has also been produced in animals intratracheally injected with small diameter glass fibers (63).

POPULATION AT RISK

Asbestos has over 3,000 commercial uses and is ubiquitous in the general environment. Because of the mineral's resistance to thermal and chemical degradation, exposures may take place starting from initial mining of the fibers through manufacture, use, and eventual burial of asbestos containing waste.

Mining and milling of asbestos in the United States is not extensive: fewer than a thousand workers are employed (148). However, amphibole

minerals and, to a lesser extent, serpentines, are sometimes found as contaminants of other types of ore bodies, such as talc, vermiculite, crushed stone aggregates, and in ores from various metal mining operations (19)(64)(115) (140). There have been no systematic studies of mining operations in the United States to identify specific ores containing asbestos as contaminants and the degree to which workers are exposed.

Estimates of the number of workers exposed to asbestos in primary manufacturing of asbestos products are given in Table II-10. In the primary manufacturing sector approximately 18,000 workers are estimated to be potentially exposed; however, this number could be as high as 37,000 (17). A large variety of asbestos products and materials produced in primary manufacturing are fabricated and processed with other materials in secondary industries to produce the more than 3,000 end products containing asbestos. The secondary fabrication and processing industry is very large and has been estimated to employ more than 300,000 workers (17).

By far the largest number of workers with potential asbestos exposures may be found in industries which utilize asbestos products such as the construction industry, the automobile servicing industry (including remanufacturing of

Table II-10
ESTIMATES OF WORKERS EXPOSED
TO ASBESTOS IN PRIMARY
MANUFACTURING

Manufacturing Sector	Estimated Number of Potential Exposed Workers
Asbestos cement pipe	1,755
Asbestos cement sheet	980
Friction materials	5,605
Floor coverings	3,500
Asbestos paper products	2,120
Packing and gaskets	1,125
Paint, coating and sealant	815
Asbestos textiles	1,800
Total	17,700

Source: (17)

asbestos containing parts), and the shipbuilding and repair industry. In the construction industry, including those doing demolition and repair, an estimated 180,000 to 408,000 workers are potentially exposed to asbestos. The automobile servicing industry includes brake and clutch servicing garages, rebuilding and refacing friction components, and repackaging of friction products. Within this sector, 2 million workers are potentially exposed to asbestos (17). Approximately 3,800 workers are potentially exposed to asbestos in shipbuilding and repair.

A total of 2.3 to 2.5 million workers are estimated to be currently (potentially) exposed to asbestos. However, because of the long latency (20 to 30 years) required before asbestos related diseases become clinically manifest, past asbestos workers must also be considered at risk. These estimates are especially difficult to develop and are subject to controversy (29). Nonetheless, large numbers of previous asbestos workers are now completing their latency period and are at risk of asbestos related diseases.

EPIDEMIOLOGY

Early Observations

Asbestosis

The first well documented case of asbestosis was reported by H. Montague Murray in 1906, although there were several anecdotal reports prior to this time (66)(95). Murray documented

a case of pulmonary fibrosis at autopsy in a worker engaged in the production of asbestos textiles. This worker reported that he was the sole survivor of 10 men who started with him in the carding room; the others had died.

Following the report by Murray, Pancoast et al. (1917) reported 17 cases of pulmonary fibrosis in a Pennsylvania plant (105). In 1924, Cooke published another detailed autopsy report of a 33-year-old woman suffering from asbestosis (14). Necropsy findings included pulmonary fibrosis, pleural thickening, pleural calcification, and heart enlargement. Further cases were reported by Mills in 1930, Donnelly (1933), Lynch and Smith (1931), Seiler and Gilmour (1931), Wood and Gloyne (1930), Oliver (1927), Simson (1928), Stewart (1928), and Pancoast and Pendergrass (1926) (21)(70)(88)(104)(106)(120)(134)(141)(164). By 1930, more than 75 asbestosis cases had been reported in the literature.

Early case reports stimulated concern and in 1928 the first detailed epidemiologic study of asbestos workers was undertaken by the Ministry of Labour in Great Britain. Results were published by Merewether and Price in 1930 (84). This was a cross-sectional chest x-ray study of 363 workers engaged in production of asbestos textiles. Of this group, 95 (26.2%) were found to have pulmonary fibrosis and the prevalence of fibrosis with 20 or more years employment was over 80%.

In the United States, Donnelly (1936) reported a cross-sectional chest x-ray study of 151 asbestos workers which found a pulmonary fibrosis prevalence of 59% among workers employed 4 years or more (22). Schull (1936) reported chest x-ray studies of 100 workers dismissed from North Carolina asbestos plants due to disability and found a 55% prevalence of moderate or advanced asbestosis (131).

In 1937 the U.S. Public Health Service undertook the first detailed epidemiologic study of asbestos workers in the United States with results published by Dreessen et al. in 1938 (23). A total of 511 employees were studied in this cross-sectional study and worker exposures were estimated by the impinger method. A relationship was found between extent of asbestos exposure and clinical symptoms of asbestosis although many workers had only short periods of exposure at the time of the study. This study resulted in a recommended occupational exposure

limit of 5 million particles per cubic foot of air (mppcf) in the United States.

Lung Cancer and Mesothelioma

The first indication that asbestos might be a human carcinogen came in 1935. Lynch and Smith (in the United States) and Gloyne (in England) independently reported three cases of lung cancer detected during autopsy studies of asbestos workers (34)(71). All three workers had died of asbestosis. Other case reports followed by Egbert and Geiger in 1936, Gloyne in 1936, and Nordmann in 1938 (26)(33)(102). In the 1947 annual report of the Chief Inspector of Factories in England, Merewether stated that of 365 asbestosis deaths, 65 (17.8%) also had cancer of the lung at autopsy (83). This compared to a prevalence of lung cancer of only 1.3% for cases certified at death as having silicosis.

Despite early suggestions, the first detailed epidemiologic study to conclusively demonstrate an association between asbestos exposure and lung cancer was not published until 1955 by Doll (20). Doll studied the mortality experience of a cohort of 113 asbestos textile workers employed more than 20 years. Among this group, 11 lung cancer deaths were observed compared to only 0.8 expected—based on the mortality experience of England and Wales.

Asbestos exposure is associated with mesothelial tumors of pleural and peritoneal tissues. Lee and Selikoff have reviewed early reports associating asbestos exposures and mesothelioma (66). The first cases were reported in 1946 by Wyers (165). However, conclusive evidence of an association between asbestos exposure and mesothelioma was not available until 1960 when Wagner et al. reported 33 pleural mesotheliomas in the crocidolite mining area of South Africa (152).

Mortality

Epidemiologic studies have repeatedly demonstrated an association between asbestos exposure and increased mortality due to asbestosis, lung cancer, pleural and peritoneal mesothelioma, and gastrointestinal cancer. In some studies, asbestos exposure has also been associated with increased risks for laryngeal cancer and cancer of the buccal cavity and pharynx. Table II-11 contains a brief summary of important mortality studies and significant findings. In this section, mortality studies are reviewed with emphasis on

asbestosis and lung cancer risk differences by fiber type, industry, and smoking patterns.

Mixed Fiber Exposures

In most plants processing asbestos, several different types of asbestos may be used or have been used in the past. Typically, chrysotile and one or more amphiboles are used.

Asbestos insulation workers have been extensively studied in the United States and other countries. Selikoff et al. studied the mortality experience of 632 insulation workers followed between 1943 and 1962 and observed 45 lung cancer deaths whereas only 6.6 were expected (123). Of the 255 deaths in this cohort, 28 (11%) were due to asbestosis and 3 (1.2%) to mesothelioma. An SMR of 309 was observed for cancer of the stomach, colon, and rectum (although it was based on a small number of observed cases).

A much larger cohort of 17,800 insulation workers was followed by Selikoff et al. between 1967 and 1976 (126)(127). Among this cohort, 2,271 deaths were observed including 429 lung cancers (SMR-406), 78 asbestosis deaths, and 49 deaths due to mesotheliomas. Significant increased mortality was also observed for cancers of the esophagus, stomach, colon-rectum, larynx, buccal cavity and pharynx, and kidney. Only 2 of the 78 asbestosis deaths occurred prior to 20 years from onset of employment, based on death certificate information. Review of all available autopsy, surgical, and clinical material indicated an additional 90 deaths were due to asbestosis, 57 to lung cancer, and 126 to mesothelioma.

Elmes and Simpson studied the mortality of 162 insulation workers in Belfast between 1940 and 1975 (27)(28). Among this cohort, 122 deaths were observed including 16 (13.1%) due to asbestosis and 13 (10.7%) to mesothelioma. A large excess due to respiratory cancer was observed.

There are several important studies of mortality among textile workers exposed to mixed asbestos types. In an early study in the United States published in 1963, Mancuso and Coulter observed more than a threefold excess risk of lung cancer among workers producing textile and friction products (73). Fourteen percent of 195 deaths were due to asbestosis and 2 (1%) were due to mesotheliomas.

Mortality among employees in the plant initially studied by Doll in 1955 has been in-

Table II-11
SUMMARY OF MORTALITY STUDIES OF ASBESTOS EXPOSED POPULATIONS

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Doll	1955	113 textile workers employed 20 or more years	Mixed	Retrospective cohort 1922-1953	11 lung cancers observed versus 0.8 expected, 14 death certificates mentioned asbestosis.
Mancuso and Coulter	1963	1,495 workers producing textile, friction products	Mostly chrysotile	Retrospective cohort, 1940-1960	28 asbestosis deaths, 19 lung cancers observed versus 5.6 expected, 5 peritoneal neoplasms (2 were mesotheliomas).
Selikoff, Churg and Hammond	1964	632 insulation workers with 20 or more years employment	Mixed	Retrospective cohort, 1943-1962	12 asbestosis deaths, 45 lung cancers observed versus 6.6 expected. Increased gastrointestinal cancer, 3 pleural mesotheliomas.
Knox et al.	1965, 1968	1,014 textile workers	Mixed	Retrospective cohort, 1922-1966	27 lung cancers observed versus 10.75 expected, 42 with asbestosis on death certificate. Authors suggested reduced risks after controls added in 1933.
Newhouse	1969, 1973	4,500 textile workers	Mixed	Retrospective cohort, 1933-1968	Significant excesses for lung cancer among workers in highest exposure category; 24 mesotheliomas among males.
Newhouse et al.	1972	922 female textile and friction product workers	Mixed	Retrospective cohort, 1942-1968	14 lung cancers observed versus 0.5 expected in those working 2 years in highest exposure jobs. Approximately threefold excess of respiratory disease mortality in this group. Overall 1 mesothelioma.

Table II-11
SUMMARY OF MORTALITY STUDIES OF ASBESTOS EXPOSED POPULATIONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Selikoff, Hammond and Churg	1968	370 insulation workers with >20 years employment	Mixed	Retrospective cohort, 1963-1967	Observed strong interactive effect between asbestos exposure and smoking for lung cancer; 10 mesothelioma deaths observed and 15 asbestosis deaths.
Elmes and Simpson	1971, 1977	162 insulation workers	Mixed	Retrospective cohort, 1940-1975	16 asbestosis deaths, 13 mesotheliomas. Large excess risk for respiratory cancer throughout follow-up period.
McDonald, et al.	1971, 1974, 1979, 1980,	11,379 asbestos miners and millers	Chrysotile	Retrospective cohort, 1926-1975	Among those achieving >20 years latency, overall lung cancer SMR = 125, with 42 pneumoconiosis deaths and 11 mesothelioma deaths. Linear dose-response observed for lung cancer and pneumoconiosis.
Enterline and Henderson	1972, 1978	1,075 retired asbestos product worker's	Chrysotile and amphiboles	Retrospective cohort, 1941-1973	Lung cancer SMR = 270; 19 asbestos deaths. Linear dose-response observed for lung cancer with SMR = 198 at 62 mppcf-yrs. and SMR = 778 at 976 mppcf-yrs.; 2 mesothelioma deaths.
Selikoff et al.	1973, 1979	17,800 insulation workers	Mixed	Retrospective cohort, 1967-1976	429 lung cancers observed versus 105.6 expected; 78 asbestosis deaths and 49 mesotheliomas.
Meurman et al.	1974	1,092 asbestos mine and mill workers	Anthophyllite	Retrospective cohort, 1936-1974	21 lung cancers observed versus 13 expected; 13 asbestosis deaths but no mesotheliomas. A strong interactive effect on lung cancer with smoking and asbestos exposure was observed.

Table II-11
SUMMARY OF MORTALITY STUDIES OF ASBESTOS EXPOSED POPULATIONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Peto et al. and Peto	1977, 1979	1,106 textile workers employed >10 years	Mixed	Retrospective cohort	36 respiratory cancers observed versus 19.3 expected among those only employed in controlled areas. Significant excess of non-malignant respiratory diseases.
Weiss	1977	264 paper and millboard workers	Chrysotile	Retrospective cohort, 1945-1974	2 asbestosis deaths among a total of 66 deaths. No excess of lung cancer but numbers were small; no mesotheliomas reported.
Jones et al.	1976, 1979	1,088 gas mask workers during WW II	Crocidolite	Retrospective cohort, 1939-1976	12 lung cancers observed versus 6.3 expected in women; 17 mesothelioma deaths. Linear dose-response for mesothelioma with employment duration; 3 mesotheliomas observed among those exposed 5-10 months.
Edge	1976, 1979	429 shipyard workers with pleural plaques	Mixed	Prospective follow-up 1968-1974	19 broncogenic cancers observed versus 4.0 expected; 23 mesotheliomas observed. Shipyard workers with plaques had 2.5 times lung cancer risk when compared to matched controls without plaques.
Hughes and Weill	1979	5,645 asbestos cement workers >20 years latency	Chrysotile and crocidolite	Retrospective cohort, 1940-1973	23 lung cancers observed versus 9.3 expected among those with cumulative fiber exposures >100 mppcf/yr.; 2 pleural mesotheliomas observed versus 4.4 expected among those not exposed to crocidolite.

Table II-11
SUMMARY OF MORTALITY STUDIES OF ASBESTOS EXPOSED POPULATIONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Sheers	1979	410 dockyard workers with pleural plaques or pleural fibrosis	Mixed	Prospective follow-up 1967-1976	6 mesothelioma deaths among those with plaques and 2 with only pleural fibrosis. Author suggested pleural plaques are of greater biological significance than simply a marker of exposure.
Scidman, Selikoff and Hammond	1979	820 men producing insulation between 1941-1945	Amosite	Retrospective cohort, 1961-1975	83 lung cancers observed versus 23.9 expected. Among 61 men employed <1 month, 3 lung cancers observed versus 1.3 expected. 4 mesotheliomas by death certificate diagnosis but an additional 10 identified using necropsy data. 15 deaths observed due to asbestosis.
Hammond, Selikoff	1979	12,051 insulation workers with >20 years latency	Mixed	Retrospective cohort, 1967-1976	Asbestos workers who did not smoke had a fivefold risk of lung cancer compared to nonsmoking controls. Smoking asbestos workers had 53 times the lung cancer risk of nonasbestos exposed persons who also did not smoke.
Robinson, Lemen and Wagner	1979	3,276 workers producing textile, friction products	Mostly chrysotile	Retrospective cohort, 1940-1975	Overall lung cancer SMR = 136 for males and 824 among females. Some increasing trends in lung cancer with employment duration. Large excesses due to asbestosis. 17 mesothelioma deaths observed.

Table II-11
SUMMARY OF MORTALITY STUDIES OF ASBESTOS EXPOSED POPULATIONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Nicholson et al.	1979	544 chrysotile miners and millers, >20 years employment	Chrysotile	Retrospective cohort, 1961-1977	28 lung cancers observed versus 11.1 expected; 26 cases of asbestosis observed; 1 pleural mesothelioma observed.
Dement et al.	1980	768 textile workers	Chrysotile	Retrospective cohort, 1940-1975	26 lung cancers observed versus 7.47 expected; 15 asbestosis deaths and 1 mesothelioma death. Linear dose-response for lung cancer with SMR = 223 at cumulative exposures <30 fiber/cc x yrs.
Brown, Dement, and Wagoner	1979	398 talc miners and millers	Anthophyllite and tremolite	Retrospective cohort, 1947-1975	9 lung cancers observed versus 3.3 expected. Significant excess due to nonmalignant respiratory diseases; 1 mesothelioma death.

vestigated by Knox et al. (59)(60), and more recently by Peto et al. (108)(109). Peto studied 1,106 men and women who had worked 20 or more years in asbestos exposed areas. Among those who were first employed after 1933 (when control regulations were enacted), 31 lung cancer deaths were observed whereas 19.3 were expected. Additionally, 35 deaths were observed due to nonmalignant respiratory disease versus 25 expected, and there were 5 deaths due to pleural mesothelioma. Dust exposures in this plant were reported to be generally above 5 fiber/cc until about 1970.

Newhouse (96)(97) and Newhouse et al. (98) have studied patterns of mortality among 4,600 male and 922 female workers in a plant which chiefly produced asbestos textiles but later asbestos insulation products. Exposures were classified as low to moderate (5-10 fibers/cc) and severe (>10 fibers/cc). Among males, there were 46 mesothelial tumors and an SMR for lung cancer of 538 was observed for those employed more than ten years in the severe exposure group. In those with lowest exposure, a lung cancer SMR of 154 was observed. Deaths from chronic respiratory diseases were 1.8 times expected in the highest exposure group. A remarkable cancer SMR was observed among females in the highest exposure group (21 observed versus 0.8 expected). Both males and females were found to have smoked more than the comparison population; however, this could only account for 10% to 20% of the observed excess lung cancer mortality.

The asbestos cement product industry is one of the largest consumers of asbestos in the United States. In addition to their asbestos exposure, workers in this industry may also be exposed to low levels of crystalline silica and other materials associated with cement dust. Weill et al. reported mortality patterns among 5,645 asbestos cement product workers with a minimum of 20 years since initial employment (156). Exposures for the cohort were estimated and expressed as mppcf \times yrs. Among those exposed to greater than 100 mppcf \times yrs., 23 lung cancers were observed versus 9.3 expected. No excess lung cancer risk was reported among those with cumulative exposures less than 100 mppcf \times yrs. Two pleural mesothelioma deaths were observed. Weill et al. reported that exposure to crocidolite in addition to the (predominant)

chrysotile used in cement products increased the lung cancer risk in comparison to chrysotile exposure alone. The unusually low SMRs for all causes regardless of exposure category suggest that cohort follow-up and death certificate ascertainment was less complete than desired.

Crocidolite

Wagner et al., in 1960, reported 33 pleural mesotheliomas among men working in crocidolite mines and mills and the population living in the vicinity of these mills in the Northwest Cape Province of South Africa (152). The high incidence of mesotheliomas in this area has been confirmed by other investigations (13)(39)(155).

Crocidolite was commonly used in the production of gas mask canisters during World War II and mortality among these workers has been investigated. Jones et al. studied the mortality of 1,088 workers exposed between 1940 and 1945 and followed through 1976 (46)(47). Twenty-two pleural and 7 peritoneal mesotheliomas were observed and a linear relationship was observed between employment duration and the risk of mesothelioma. There was also a modest excess of bronchial carcinoma. Similar results have been reported by McDonald and McDonald who studied a smaller cohort of gas mask workers in Canada and found that 7% of all deaths were due to mesotheliomas (75).

Amosite

Mortality patterns among a cohort of workers producing amosite asbestos insulation between 1941 and 1945 have been reported by Selikoff et al. (125) and more recently by Seidman et al. (118)(119). This group of 820 men were observed over a 35 year period during which 528 deaths occurred: by death certificate information 15 (2.8%) were due to asbestosis and 1 was due to mesothelioma. Review of available surgical, pathological, and clinical data for this group identified 13 additional mesotheliomas and 15 additional cases of asbestosis not listed on death certificates. Overall there were 83 lung cancers observed whereas 23.1 were expected and among those employed less than one month, 3 lung cancers were observed versus 1.3 expected. Anderson et al. have observed four confirmed cases of mesothelioma among household contacts of workers at this plant (1).

Anthophyllite and Tremolite

The only location in the world where anthophyllite has been commercially mined and processed is Finland. These ores are also known to contain smaller quantities of tremolite. Mortality among workers in two Finnish mines and mills has been studied by Meurman et al. (86) (87). In their first report, 1,092 workers were followed from 1936 until 1974. A relative risk for lung cancer of 1.6 was observed and there were 13 (5.2%) asbestosis deaths but no deaths due to mesothelioma. Their subsequent study concerned 793 workers with known smoking histories with 10 additional years of follow-up. A relative risk for lung cancer of 19 was observed for smoking asbestos workers and 1.6 for asbestos workers who did not smoke. Asbestosis mortality was found to be equally frequent among smokers and nonsmokers. All lung cancer cases with more than 10 years of exposure were also found to have asbestosis.

Chrysotile

Chrysotile is the major asbestos fiber type used in the United States, but most of this fiber is imported from Canada. The mortality of Quebec chrysotile miners and millers has been extensively studied by McDonald et al. (76) (79-81). The most recent report for this cohort included 10,939 men who had been employed one or more months and followed between 1926 and 1975. An overall SMR for lung cancer of 125 was observed; 42 deaths were due to asbestosis and 11 to mesothelioma. A nearly linear dose-response relationship was reported for lung cancer. Increased mortality was also observed for cancer of the stomach and esophagus but no other gastrointestinal sites. Similar patterns of lung cancer and asbestosis mortality have been reported by Rubino et al. in Italian chrysotile miners and millers where an SMR for lung cancer of 206 was observed among those with sufficient latency (117).

The McDonald et al. studies demonstrated a low lung cancer risk even in the highest exposure group. Nicholson et al. have reported larger excesses from lung cancer and asbestosis in their study of chrysotile miners and millers in Quebec (99). This latter study cohort consisted of 544 miners and millers with at least 20 years seniority and followed between 1961 and 1977. A total of 28 lung cancers were observed versus 11.1 expected (SMR = 252). There were 30

deaths due to noninfectious respiratory diseases whereas only 6.7 were expected. Of these 30 deaths, 26 were due to asbestosis. Only one mesothelioma (pleural) was observed.

Mortality among chrysotile asbestos miners and millers in the Urals has been investigated by Kogan et al (61). The overall cancer mortality risk was found to be 1.6 times that for the general male population and was higher in mining than in milling. Among males, the relative risk for lung cancer was 2.0 and ranged from 1.4 to 2.1 for females. The lung cancer risk was considerably greater in older age groups having the longest latency. No mesotheliomas were reported; however, Kogan et al. attributed this to insufficient experience of pathologists in that geographic area (61). Nonetheless, the low mesothelioma risk is consistent with other studies of chrysotile-exposed populations.

There have been several studies of factory populations exposed only to chrysotile. Weiss studied a small cohort of 264 workers in a plant producing asbestos millboard and reported no excess cancer mortality (160). However, there were only 66 deaths (2 of which were due to asbestosis) and cancer latency was not taken into account in the analysis.

A facility manufacturing asbestos textile, friction, and packing products has been studied by Robinson et al. (113). Chrysotile constituted over 99% of the total quantity of asbestos processed per year in this plant except during World War II; the remaining 1% was crocidolite and amosite. The cohort consisted of 2,722 males and 544 females followed between 1940 and 1975. Among males, an overall lung cancer SMR of 135 was observed but among females the excess lung cancer risk was much higher with an overall SMR of 824. There were 76 deaths in males due to noninfectious respiratory disease but only 16.4 expected. Again, the chronic respiratory disease risk was higher among females with an SMR of 1,555. There were 4 mesotheliomas among females and 13 in males.

Dement et al. have reported mortality among a cohort of asbestos textile workers exposed only to chrysotile (18). This cohort consisted of 768 white males employed at least 6 months and followed between 1940 and 1975. There were 26 lung cancers observed versus 7.47 expected. Of the 191 deaths in this cohort, 15 (7.9%) were due to asbestosis or pulmonary fibrosis and 1 (0.5%) was due to a peritoneal

mesothelioma. Linear relationships were demonstrated between cumulative fiber dose and the risk of mortality for lung cancer and noninfectious respiratory diseases. An SMR for lung cancer of 223 was observed for the lowest cumulative exposure category of less than 30 fibers/cc \times years.

Fibers and Asbestos-like Contamination of Other Minerals

Both serpentines and amphiboles may be found as contaminants in other mined and processed ores and may result in significant fiber exposures to workers in these operations.

Fibers and cleavage fragments of fibrous grunerite occur where ore from some iron formations are crushed and comminuted and have been found in high concentrations in Lake Superior as a result of mining and milling operations (64). Gillam et al. studied mortality among gold miners exposed to cummingtonite-grunerite and found a threefold excess risk of lung cancer and a twofold excess of nonmalignant respiratory disease, excluding influenza and pneumonia (32). However, workers in this mine were also exposed to silica. McDonald et al., in a subsequent study of the same mine, examined the mortality experience of persons with at least 21 years of employment with the company (78). This study demonstrated excess mortality due to pneumoconiosis (mainly silicosis), tuberculosis, and heart disease but no overall excess of malignant diseases was found. However, when the population was stratified by exposure, respiratory cancer was elevated (but was not statistically significant) in the highest exposure group.

Commercial talc deposits are sometimes found to contain serpentines (chrysotile, antigorite, and lizardite) and fibrous and nonfibrous amphiboles. Kleinfeld et al. demonstrated significantly increased proportionate mortality due to lung cancer and nonmalignant respiratory disease among talc miners and millers in New York State exposed to fibrous anthophyllite and fibrous tremolite (53)(58). Brown et al. have reported a further mortality of talc miners and millers in one company mining this same ore body (9). This cohort consisted of 398 workers followed between 1947 and 1975. Among this cohort, 10 respiratory cancers were observed whereas only 3.5 were expected. Approximately a threefold excess risk of nonmalignant respiratory disease was reported; however, only one

death due to mesothelioma was observed.

Effects of Smoking

Smoking and asbestos exposure are more than additive in their combined ability to increase the risk of lung cancer. Hammond et al. reported results of their 10-year follow-up of 8,220 asbestos insulation workers with known smoking status (38). The mortality experience of these workers was compared with that expected among smokers and nonsmokers of the American Cancer Society's prospective cancer prevention study. Asbestos workers who did not smoke showed approximately a fivefold risk of lung cancer compared to the nonsmoking control population. On the other hand, a more than sixtyfold risk of lung cancer was observed for smoking asbestos workers compared to nonsmoking controls. A similar multiplicative effect was observed by Selikoff et al. among a factory cohort producing amosite insulation (129).

Although less striking, cigarette smoking may also contribute to the risk of death due to asbestosis. Hammond et al. reported that asbestosis death rates of smoking asbestos workers were 2.8 times as high as that of nonsmoking asbestos workers. Meurman found less association between asbestosis mortality and smoking; he reported 7 of 42 asbestosis deaths among nonsmokers (86).

Mortality and Pleural Radiographic Changes

The relationship between pleural thickening and calcification and subsequent mortality is important insofar as surveillance of asbestos workers is concerned. Edge studied the mortality of 429 shipyard workers with plaques and compared this to matched controls without plaques (25). Among those with plaques, 23 mesotheliomas were observed and workers with plaques had 2.5 times the lung cancer risk of those without plaques. Sheers observed 6 mesothelioma deaths among 410 dockyard workers with plaques, but he found just 2 mesotheliomas in those with only pleural fibrosis (130). Neither of these studies established causality between pleural changes and subsequent development of mesothelioma or lung cancer because neither asbestos exposure or latency were controlled for in the analysis. Meurman has shown that anthophyllite asbestos workers have a high prevalence

of pleural changes but a minimal mesothelioma risk (86)(87). However, plaques and pleural thickening do indicate an asbestos exposure and this fact alone places the workers at an increased risk for lung cancer and asbestosis.

Respiratory Morbidity

All types of asbestos have been shown in epidemiologic studies to be associated with asbestosis, pleural thickening, and pleural calcification. Available evidence from cross-sectional and prospective respiratory disease studies provide little evidence that any one type of asbestos is more biologically active than another insofar as x-ray or clinical changes are concerned (149) (164). These findings are fully supported by animal bioassay data.

Important epidemiologic studies of respiratory morbidity among asbestos workers are summarized in Table II-12. In these studies, various objective measures of effect or disease outcome have been used including chest roentgenographs, spirometry, measures of diffusion capacity, and chest auscultation. Subjective data such as respiratory symptoms obtained by questionnaire have also been used. In the diagnosis of "definite asbestosis," most studies have relied upon combinations of objective and subjective data.

Mixed Fiber Exposures

Early cross-sectional studies of chest roentgenographs of asbestos workers by Merewether and Price, Donnelly, Schull, and Dreessen et al. demonstrated a striking prevalence of pulmonary fibrosis of as much as 80% for workers employed more than 20 years (22)(23)(84)(131).

Several studies have been conducted among insulation workers. Selikoff et al. studied chest films of 1,117 insulation workers exposed to chrysotile and amosite (122)(124). A 50% overall prevalence of pulmonary fibrosis was observed increasing to 90% among those employed more than 30 years. Pleural calcification showed an increasing prevalence with latency reaching 57.9% at 40 years since initial employment. Pleural fibrosis (thickening) occurred earlier than calcification. Murphy et al. also studied shipyard insulation workers and found a prevalence of asbestosis 11 times that of age matched, non-exposed controls (92)(93). Exposures among this group were thought to be low.

Cross-sectional data from an asbestos textile plant processing a mixture of asbestos types were

used by the British Occupational Hygiene Society (BOHS) in establishing occupational exposure standards (8). Among 290 workers employed after dust controls were installed in 1933, only 8 workers (2.7%) demonstrated x-ray changes considered consistent with asbestosis. Basal rates was taken as an early disease marker with a 1% risk estimated for a working lifetime of 50 years at an average exposure of 2 fibers cc. Workers at this same plant were subsequently studied cross-sectionally by Lewinsohn (67). This latter and much larger study demonstrated a significantly greater prevalence of pulmonary fibrosis; reaching 40.5% among workers employed from 30-39 years. Pleural fibrosis (thickening) was observed in 1.6% of those employed 1-9 years and in 50% of workers employed more than 40 years.

Berry et al. reported the results of a prospective study of workers employed in the same plant studied by Lewinsohn (67). This study consisted of 379 persons completing 10 or more years employment by 1971. Possible asbestosis was diagnosed based on one or more combinations of basal rates or crepitations, radiological changes, a falling transfer factor and restrictive lung function changes. Among these 379 men, 60 cases of possible asbestosis were diagnosed by the factory medical officer, whereas 85 cases were diagnosed by an independent clinician. Using plant exposure data, it was estimated that the cumulative dose necessary for a 1% incidence for crepitations, possible asbestosis, and certified asbestosis was 43 fiber/cc-yr, 55 fiber/cc-yr, and 72 fiber/cc-yr, respectively. Two cases of certified asbestosis were observed among nonsmokers and nine among ex-smokers, suggesting a contributory smoking role. Weiss reported similar findings in his study of 100 asbestos textile workers where a 24% prevalence of pulmonary fibrosis was observed in nonsmokers versus 40% for smokers (159)(161). Gregor et al. demonstrated a progression of radiological changes in asbestos workers referred to the British Pneumoconiosis Medical Panel without further asbestos exposures (36).

Lung function and chest film effects of exposure to asbestos cement dust have been studied by Weill et al. (157)(158). This study included 859 workers in two asbestos cement plants who were administered respiratory symptom questionnaires, spirometry, and chest films. Cumulative dust exposures were estimated and expressed as mppcf-yr. Both small rounded and linear opac-

Table II-12
SUMMARY OF RESPIRATORY MORBIDITY STUDIES OF ASBESTOS EXPOSED POPULATIONS

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Selikoff, Churg, and Hammond	1965	1,117 insulation workers	Chrysotile and amosite	Cross-sectional, no external controls	50% prevalence of pulmonary fibrosis. Increasing prevalence of all chest film changes with employment duration increasing to 90% prevalence at >30 years
Kilviluoto et al.	1960, 1965, 1979	Persons in Central Finland	Anthophyllite tremolite	Case series	Pleural calcification observed in persons only secondarily exposed to asbestos. Pleural changes unrelated to lung cancer mortality.
Selikoff	1965	1,117 insulation workers	Chrysotile and amosite	Cross-sectional, no external controls	Pleural calcification showed increasing prevalence reaching 57.9% among those with 40 years since first exposure. Pleural fibrosis occurred earlier than calcification, 50% of cases were bilateral.
McDonald et al.	1972	1,015 chrysotile miners and millers	Chrysotile	Cross-sectional, no externals	Shortness of breath increased with estimated cumulative dust exposure but bronchitis showed little correlation.
Becklake et al.	1972	1,105 chrysotile miners and millers	Chrysotile	Cross-sectional, no externals	FVC found to decrease with estimated cumulative dust exposure in smokers and non-smokers. Same trends seen in FEV ₁ . Obstructive impairment seen in high exposure group. Few trends in diffusing capacity.

Table II-12
SUMMARY OF RESPIRATORY MORBIDITY STUDIES OF ASBESTOS EXPOSED POPULATONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
McDonald et al.	1974	5,082 miners and millers with chest films	Chrysotile	Mortality follow-up	Increased mortality observed for those with parenchymal changes but not in those with only pleural changes, 32 deaths observed due to all respiratory diseases versus 8 expected.
Liddell et al.	1977	267 miners and millers with chest films	Chrysotile	Prospective follow-up	During 20-year period, the following cumulative incidence was reported: small opacities 16%, pleural thickening 5.3%, pleural calcification 5.3%, obliteration of c/p angle 7.3%
Weiss	1971	100 asbestos textile workers	Unknown	Cross-sectional, no external controls	Overall prevalence of fibrosis 36% with 24% prevalence in non-smokers and 40% in smokers. None of 11 nonsmokers with exposures less than 20 years showed fibrosis.
BOHS	1968	290 asbestos textile workers	Mixed	Cross-sectional, no external controls	Basal rates used as early disease marker, 1% risk estimated for a working lifetime of 50 years at 2 fibers/cc.
Lewinsohn	1972	1,287 asbestos textile workers	Mixed	Cross-sectional, no external controls	Prevalence of pulmonary fibrosis 0% with 0-9 years exposure up to 40.5% with 30-39 years exposure. Pleural fibrosis prevalence 1.6% in 0-9 years and 50% in 40-49 years exposure group.

Table II-12
SUMMARY OF RESPIRATORY MORBIDITY STUDIES OF ASBESTOS EXPOSED POPULATONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Berry et al.	1979	379 asbestos textile workers	Mixed	Prospective follow-up	6.6% of workers had "possible" asbestosis after 16 years follow-up and an average exposure of 5 fibers/cc. Cumulative exposure for 1% incidence of "possible asbestosis" for 40 years employment estimated to be 55 fibers/cc X years.
Weill et al.	1973	908 asbestos cement workers	Mixed	Cross-sectional, no external controls	Overall prevalence of small rounded opacities 1/0 or greater was 3.1%, for small irregular opacities prevalence was 2.5%. Reduced FEV ₁ , FEF ₂₅₋₇₅ and FEV ₁ /FVC ratio found in those with x-ray abnormalities.
Weill et al.	1975	859 asbestos cement workers	Mixed	Cross-sectional, no external controls	Prevalence of small rounded and irregular opacities, 4% in lowest exposure group and 30% in highest. Pleural changes 11% in lowest exposure group and 30% in highest. FVC and FEV ₁ reduced in those with x-ray changes.
Weiss and Theodas	1978	98 workers age 40 or over in two plants	Chrosotile and amosite	Cross-sectional, no external controls	Prevalence of profusion (1/1) 17.5% in chrysotile workers and 16.5% in mixed fiber workers. Pleural thickening prevalence, 17.5% in chrysotile workers and 35.4% in mixed fiber workers. Smoking found to be significant factor in those exposed to amosite.

Table II-12
SUMMARY OF RESPIRATORY MORBIDITY STUDIES OF ASBESTOS EXPOSED POPULATONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Selikoff et al.	1977	485 miners and millers	Chrysotile	Cross-sectional, no external controls	10% prevalence of all radiographic abnormalities. Pleural changes seen in 3% of all workers. Prevalence of abnormalities among those employed less than 5 years was 5% with 3% being parenchyma changes (profusion \geq 1/0).
Jones et al.	1979	204 asbestos cement workers	Mixed	Prospective follow-up 1970-1976	Progression of small opacities dependent upon both average and cumulative exposure. Lung function declines were associated with smoking and cumulative exposure. Pleural abnormalities progressed more as a function of time with little association with additional exposure.
Anderson	1979	Household contacts of factory workers	Amosite	Cross-sectional, age, sex matched controls	35.9% prevalence of x-ray abnormalities compared to a 4.6% prevalence in the control group. Pleural abnormalities more prevalent than parenchymal changes.
Gamble, Fellner, and DiMeo	1979	121 talc miners and millers	Anthophyllite and tremolite	Cross-sectional, external comparison populations	Talc workers with greater than 15 years employment had increased prevalence of pleural abnormalities compared to comparison populations, FEV ₁ and FVC reduced in association with dust and fiber exposures.

Table II-12
SUMMARY OF RESPIRATORY MORBIDITY STUDIES OF ASBESTOS EXPOSED POPULATIONS (Continued)

Author(s)	Date	Study Population	Fiber Type	Study Design	Summary of Important Findings
Irwig et al.	1979	1,801 miners and millers with chest films	Crocidolite and Amosite	Cross-sectional, no external controls	Prevalence of pleural changes increased from 2.5% for workers with less than 1 year employment to 33.6% for workers with 15 or more years. Parenchymal changes (>1/0 ILO) found in 2.3% of workers employed less than 1 year and 26.7% in workers employed more than 15 years.
Gregor et al.	1979	119 asbestos workers referred to Pneumoconiosis Medical Panel	Mixed	Prospective follow-up	One-third of workers showed progression after 6 years follow-up and no further asbestos exposure. Progression frequency higher among those with profusion >1/1 or 1/2 (ILO).
Rubino et al.	1979	56 retired chrysotile miners and millers surviving >3 years	Chrysotile	Prospective follow-up	39% of persons with abnormal films (profusion >1/0 ILO) showed progression after an average follow-up of 8 years. 7.9% of workers with normal initial films developed radiographic changes.
Murphy et al.	1971, 1978	101 shipyard pipe coverers and 95 controls	Mixed	Cross-sectional with further follow-up matched controls	Prevalence ratio of asbestosis 11 times greater than controls. Asbestosis evident after cumulative exposures of 60 mppcf-years.

ities were observed, indicating the possible role of small quantities of silica present in cement dust. Among those with a cumulative exposure less than 50 mppcf-yr, and approximately 4% prevalence of small opacities (rounded or irregular, profusion $\geq 1/0$ was observed; the prevalence of these changes increased to 30% with an exposure of more than 400 mppcf-yr. Pleural changes were seen in 11% of those in the lowest exposure category. Both FVC and FEV₁ were reduced in those with x-ray changes. There was no apparent interaction effect of cigarette smoking on the development of diffuse fibrosis.

Jones et al. studied the progression of radiographic abnormalities and lung function changes among 204 asbestos cement workers between 1970 and 1976 (48). Films were read side by side in known order and ranked according to progression. These authors concluded that: (1) progression of small opacities depended upon both average and cumulative exposure; (2) declines in lung function were related to both smoking and cumulative exposure; and (3) pleural abnormalities progressed as a function of time. Disease incidence was not estimated in relation to exposure.

Anthophyllite and Tremolite

Respiratory morbidity among Finnish anthophyllite miners and millers has been studied by Meurman et al. (87). Among 787 active employees, a threefold excess of dyspnea and a twofold excess of cough was observed among asbestos workers compared to controls. The prevalence of dyspnea was not found to be associated with smoking habits.

A high prevalence of pleural plaques has been reported among persons residing near anthophyllite mines and mills in Finland (51)(85). In two mining communities where mass roentgenological surveys were conducted, prevalences of pleural plaques of 9% and 6.5% were observed compared to less than 0.1% for the Finnish population.

Talc deposits found in upper New York State contain both anthophyllite and tremolite. Workers in talc mines and mills in this area have been shown to experience pulmonary fibrosis, pleural changes, and restrictive lung function changes (52)(54-57)(107)(132)(133). A recent cross-sectional study of lung function and chest

x-rays among talc workers in this area was reported by Gamble et al. (31). Compared with coal and potash miners, talc miners and millers were found to have an increased prevalence of cough and dyspnea along with reduced FEV₁, FVC, and flow rates. Talc workers with more than 15 years employment were found to have a 33% prevalence of pleural calcification and pleural thickening. Recent exposures in these operations were reported by Dement and Zumwalde (19). Time-weighted-average fiber exposures were found to range from 0.8 to 16.0 fibers/cc with 12-19% identified as tremolite and 38-45% anthophyllite.

Chrysotile—Radiological changes, lung function, and respiratory symptoms among Canadian chrysotile miners and millers have been extensively studied by McDonald et al. (76)(77) and Becklake et al. (4). A total of 1,015 current employees were given chest x-rays, underwent pulmonary function studies, and were administered a standard British Medical Research Council Questionnaire on respiratory symptoms. Both persistent cough and phlegm (bronchitis) and breathlessness on exercise were found to increase with exposure. The prevalence of bronchitis rose to 50% among smokers in the highest dust exposure categories. The prevalence of breathlessness was not affected by smoking but rose to greater than 40% in those with cumulative dust exposures over 800 mppcf-years. The prevalence of irregular small opacities ($>1/0$ ILO/UC) in the lowest exposure category was found to be 1.8% for the Thetford mine and 6.4% for the Asbestos mine. Prevalences increased to 26.4% for Thetford and 10.9% for Asbestos in the group with exposures more than 800 mppcf-yr. The prevalence of pleural thickening was found to be less strongly related to exposure. Among various lung function parameters measured, both FVC and FEV₁ declined more with exposure. Those with small opacities of category 2/1 or greater were found to have significantly reduced functional residual capacity, residual volume, and single breath dif-fusing capacity at rest. Only FVC and FEV₁ were reduced in those with earliest roentgenographic changes.

Cross-sectional respiratory disease studies have been conducted among chrysotile miners and millers in Newfoundland and Corsica (7)(121). Selikoff studied 485 current employees

of a chrysotile mine in Newfoundland and found a 5% prevalence of parenchymal abnormalities (ILO U/C \geq 1/0) (121). This prevalence increased to 11.5% among those employed more than 10 years. The prevalence of pleural changes was less than that observed for parenchymal changes.

Boutin et al. studied chest films of 16 ex-workers of chrysotile mines and mills in Corsica which had been closed in 1965 (7). Compared with controls, chrysotile miners and millers had 2.4 times the risk of parenchymal abnormalities and 2 times the risk of pleural abnormalities. Exposure levels among those workers were extremely high, ranging from 85 to 267 mppcf.

The above studies of chrysotile asbestos workers have been cross-sectional by design and have likely underestimated risks since: (1) those who develop severe disease are likely to have already left employment, and (2) chest film changes may develop after termination of employment, or changes may be progressive without additional exposure. Liddell et al. studied chest film changes in a 20-year longitudinal study of chrysotile miners and millers (62). These authors observed a 20-year cumulative incidence for small irregular opacities of 16%, a pleural calcification incidence of 5.3%, and a pleural thickening incidence of 5.3%. Only the incidence of small opacities was strongly associated with smoking. Rubino et al. studied the progression of chest film changes among retired chrysotile asbestos miners and millers and found that 39% of those who had initial films with a profusion of 1/0 or greater, demonstrated progression without further exposure (116). Becklake et al. also studied radiological changes after withdrawal from asbestos exposure (5). Parenchymal progression was observed in 7% of the films, pleural progression in 19.8%, and both parenchymal and pleural progression in 2.3%. These changes were found to be independent of age and smoking, but parenchymal "attacks" occurred more among those with higher asbestos exposure prior to employment termination.

Relationships between radiological findings and subsequent mortality among chrysotile miners and millers have been studied by Liddell and McDonald (69). This study consisted of 4,559 whose latest film had been read according to the UICC/Cincinnati classification system with mortality follow-up from time of film assessment through 1975. Overall, this cohort ex-

perience significantly increased mortality for all causes (SMR = 144), lung cancer (SMR = 177), pneumoconiosis (31 cases), other respiratory diseases (SMR = 127), diseases of the heart (SMR = 136), cancer of the esophagus or stomach (SMR = 170), and cerebrovascular diseases. There were 5 pneumoconiosis deaths among those classified as having normal radiographs; however, the risk of death due to pneumoconiosis was 11.75 times greater among those with "less-than-normal" films. The lung cancer relative risk for those with chest film changes was 3.24 and most who died of lung cancer were found to be smokers. Small parenchymal opacities were present in most but not all persons whose deaths were attributed to lung cancer. The authors concluded that the chest radiograph was useful for surveillance of asbestos workers but was limited due to radiological progression after withdrawal from exposure and by the carcinogenic risk associated with dust retained in the lung.

PATHOLOGY

Pleural Plaques

Hyaline plaques of the parietal pleura occur in association with exposure to all commercial types of asbestos. They are more common than the pulmonary parenchymal lesions of asbestosis, thus their presence does not necessarily imply coexistent asbestosis. The majority occur in men, 20 years or more after first exposure. The plaques almost invariably involve the parietal pleura; less commonly they are found on the visceral pleura or parietal pericardium. They are usually bilaterally symmetrical and appear as well circumscribed, pearly white or creamy, fibrotic elevations of the pleura (Figure II-11). Their surface is smooth and glistening with either a flat, plateau-like or nodular contour. They range in size from a few millimeters to several centimeters in diameter. Most commonly they are found following the lines of the lower ribs posteriorly or on the diaphragm. On cut section, they have the consistency of cartilage. Histologically, the plaques are composed of avascular and acellular bundles of hyalinized collagen arranged in a reticulated mesh or "basket weave" pattern (Figure II-12). Some of the more nodular plaques show a whorled pattern of collagen fibers. Focal

calcification is fairly common and elastic fibers are sometimes demonstrable within the plaque (112). Although the plaques are almost acellular, lymphocytes and plasma cells may be present around blood vessels beneath the plaque. The origin of the plaque is not known; histological studies suggest an extrapleural rather than a pleural origin (145). Asbestos bodies are rarely seen in pleural plaques, though they can usually be detected in the underlying pulmonary parenchyma (40)(112). Short, uncoated fibers may be present in a proportion of plaques (40) (65). Pleural plaques rarely, if ever, undergo malignant change.

Asbestosis

In early or mild cases of asbestosis, the lungs may be of normal size and shape; in advanced

cases, they show a marked reduction in volume. The visceral pleura is usually pale, opaque, and thickened, particularly over the lower lobes. Adhesions between the visceral and parietal pleura may be present. In the absence of other exposures, pleural pigmentation is usually slight.

The lungs may appear grossly normal in cases showing histological evidence of mild disease. However, on careful palpation, it is usually possible to detect an increased firmness of the parenchyma. With advancing disease, the lungs are dark tan in color and show a pale reticular fibrosis. Characteristically, the fibrosis is most prominent in the lower lobes and dependent parts of the upper and middle lobes. In the late stages of the disease, the lungs have firm, spongy texture and show dense fibrosis with areas of cyst formation (honeycombing). The honeycomb



Figure 11-11. Diaphragmatic pleura of 88-year-old ex-construction worker. Numerous dome shaped and flattened, ivory colored plaques are seen over both hemidiaphragms.

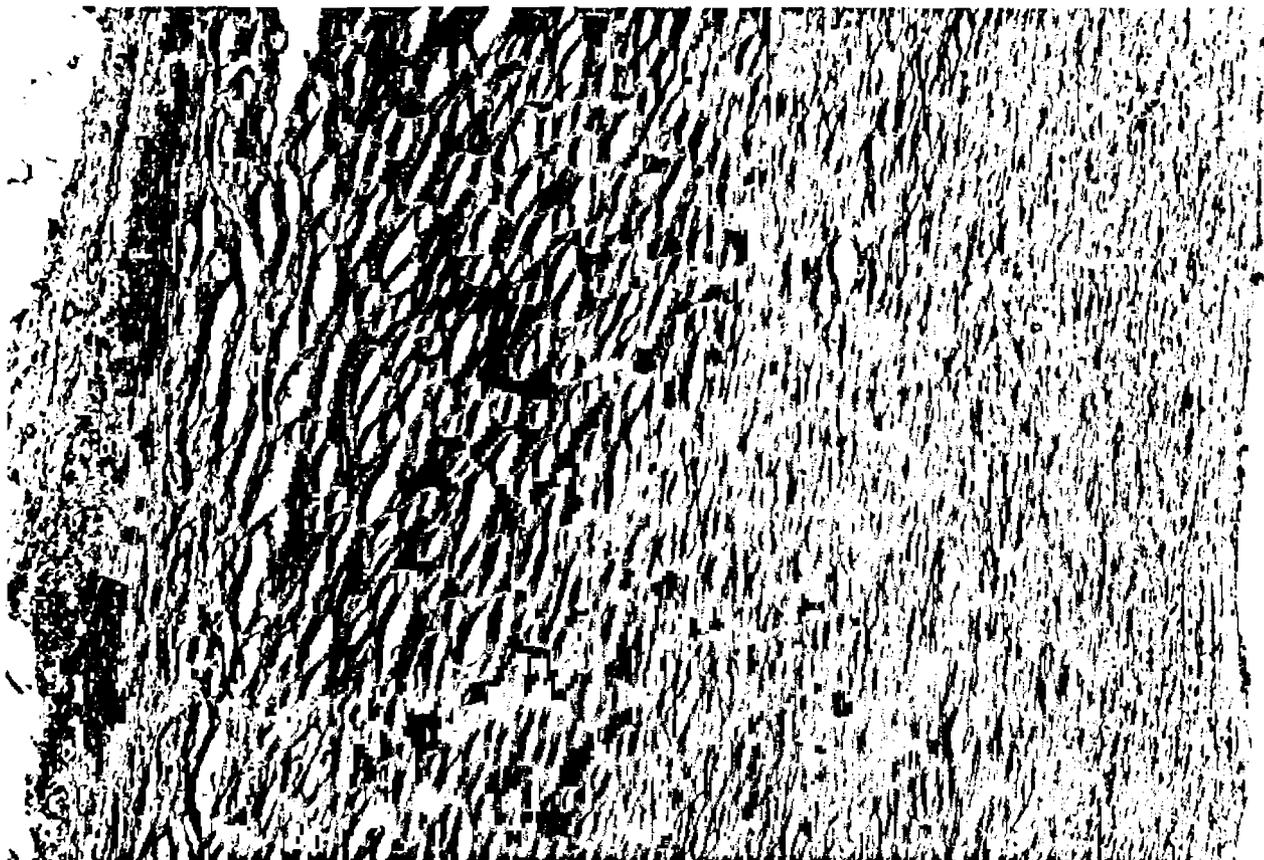


Figure II-12. Histological section of pleural plaque. The plaque is composed of acellular bundles of collagen fibers arranged in a "basket weave" pattern. Hematoxylin and eosin \times 64.

cysts vary in size from a few millimeters to a centimeter or more in diameter and are most prominent in the lower lobes and subpleural areas of the lungs (Figure II-13, A & B). Emphysema is unusual and, when present, is not related to asbestos exposure. Massive fibrosis is a less common feature of asbestosis and probably results from mixed dust exposure. Necrotic nodules similar to Caplan's lesions in coal workers have been described in patients with asbestosis and circulating rheumatoid factor (91).

Microscopically, the earliest lesion attributable to asbestos inhalation involves the respiratory bronchiole. Fibers deposited on the walls of respiratory bronchioles and adjacent alveoli stimulate a macrophage response. Depending on fiber size, giant cells may form. The macrophagic response is followed by the deposition of

reticulin and collagen in the walls of the respiratory bronchioles (Figure II-14). Asbestos bodies and fibers are found in association with the lesions of the respiratory bronchioles and within alveoli. A similar lesion has been described in cigarette smokers (100). The early lesion of asbestosis differs from the respiratory bronchiolitis of cigarette smokers only with respect to the presence of asbestos bodies. The diagnosis, therefore, of asbestosis depends upon the recognition of asbestos bodies within the lesion.

As the disease evolves, the fibrosis extends out to involve the walls of adjacent alveoli. Eventually, adjacent acini are affected resulting in a diffuse interstitial fibrosis (Figure II-15). With further progression of the disease, the pulmonary architecture becomes distorted. Intra-alveolar fibrosis leads to obliteration of alveolar spaces



Figure II-13 (A). Freeze dried whole lung section from 51-year-old male plumber exposed to asbestos lagging for 16 years. There is marked honeycombing of the mid and lower zones.

and eventually to areas of conglomerate fibrosis (Figure II-16). Despite the obliteration of alveolar spaces, the outline of the walls of the alveoli usually remain intact and can be demonstrated with elastic stains (138). Eventually, fibrous-walled (honeycomb) cysts form (Figure II-17). The cysts are lined by flattened or metaplastic epithelial cells of ciliated cuboidal, goblet, or squamous type. These changes are nonspecific and may occur in the late stages of pulmonary fibrosis, whatever the etiology. This pathogenetic

sequence of events forms the basis for a grading system developed by a committee of U.S. pulmonary pathologists assembled under the auspices of the National Institute for Occupational Safety and Health and the College of American Pathologists (16).

The above features appear to be common to all the commercially available types of asbestos. Several other types of tissue response have been described in association with asbestosis. These include chronic inflammatory cell infiltrates, desquamative interstitial pneumonia (15), and the formation of intra-epithelial eosinophilic hyaline bodies (62). These features are not specific for asbestos.

Asbestos Bodies and Fibers

Two types of fibers are encountered in the lungs; uncoated fibers that resemble the inhaled particle and coated fibers or asbestos bodies. The ratio of uncoated fibers to coated bodies is high, ranging from 5:1 to 10,000:1 (10).

Asbestos bodies are an index of asbestos exposure and are considered an essential feature for the histological diagnosis of asbestosis (16). They may be formed in the lungs as early as two months after first exposure (135). Asbestos bodies tend to form on the larger fibers, i.e., those greater than $5\mu\text{m}$ in length and result from the deposition of iron-protein complexes on the core fiber by alveolar macrophages (143). In hematoxylin and eosin stained sections they appear as golden brown segmented structures with a clear central core fiber. In Perl's iron stained sections they appear blue. The morphology of the coating is variable, with club-shaped or beaded bodies predominating (Figure II-18). Similar structures may form around other minerals such as carbon, ceramic aluminum silicate fibers, and fiberglass, and they have been termed ferruginous bodies (37)(42). They usually lack the clear central core of a typical asbestos body. These types of bodies are relatively uncommon, however, and for practical purposes, it can be assumed that a typical asbestos body contains an asbestos fiber. Although all major commercial types of asbestos can produce asbestos bodies, the majority of the core fibers, when analyzed by selected area electron diffraction, are found to be amphibole asbestos (11). Several procedures exist for the quantification and identification of fibers in tissues (11)(16)(137)(150). The majority of these fibers are too small ($<5\mu\text{m}$ in length) to be

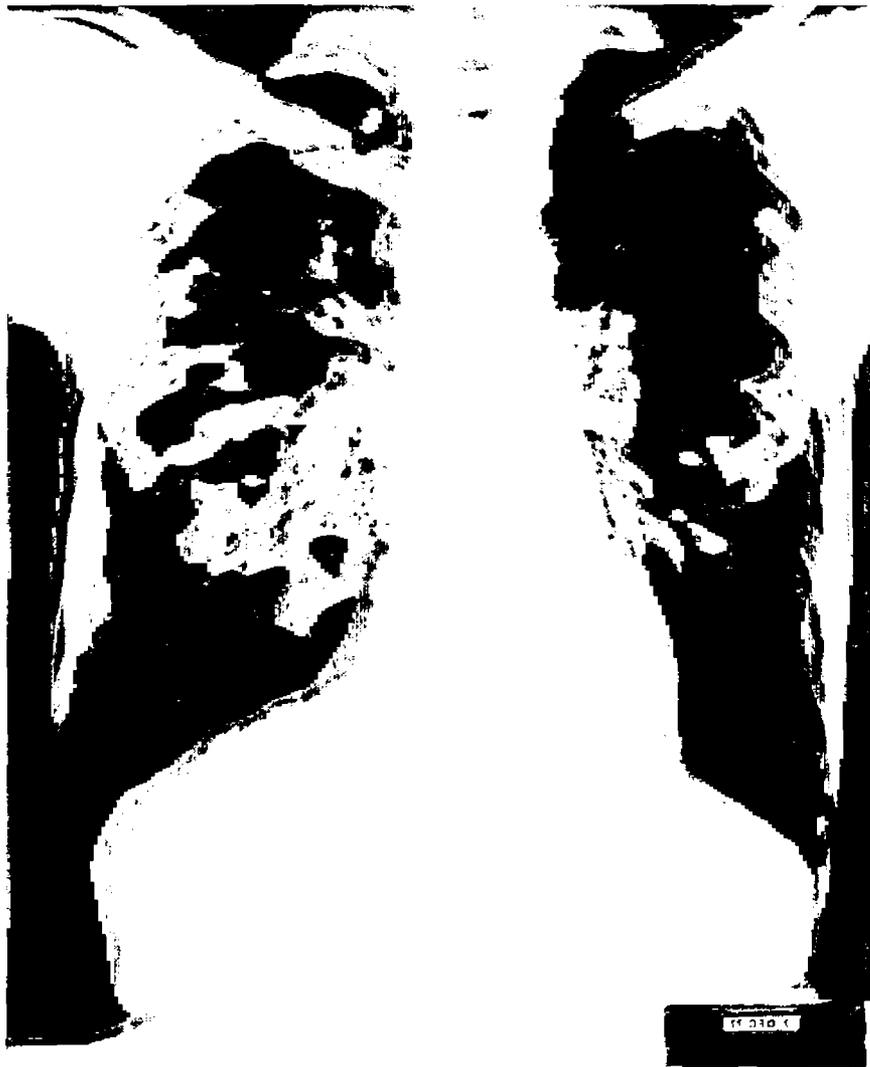


Figure II-13 (B). Roentgenogram showing marked interstitial disease with honeycombing which is most severe in the mid zones.

resolved by the light microscope. Electron microscopical studies on selected cases have shown that occupationally exposed workers have pulmonary asbestos fiber counts orders of magnitude greater than the general population (16)(163). The value of these techniques is to establish exposure and to identify the mineral type and should not be considered a substitute for more conventional diagnostic methods. Currently, the role of the short fibers in the pathogenesis of asbestosis and asbestos-associated lung cancer has not been resolved.

Lung Cancer

The association between asbestos exposure,

smoking, and lung cancer is now firmly established. The majority of asbestos-associated bronchial carcinomas arise in lungs that also show asbestosis. Autopsy and mortality studies indicate that the prevalence of lung cancer in persons with asbestosis ranges from 12-55% (42) (136).

The lung cancers associated with asbestos exposure occur at a slightly earlier age than in nonexposed individuals (74). They arise in relation to the fibrotic lesions and are thus more common in the periphery of the lower lobes (49)(162). All histological types of cancer occur with most (41)(42)(162), but not all (49), studies

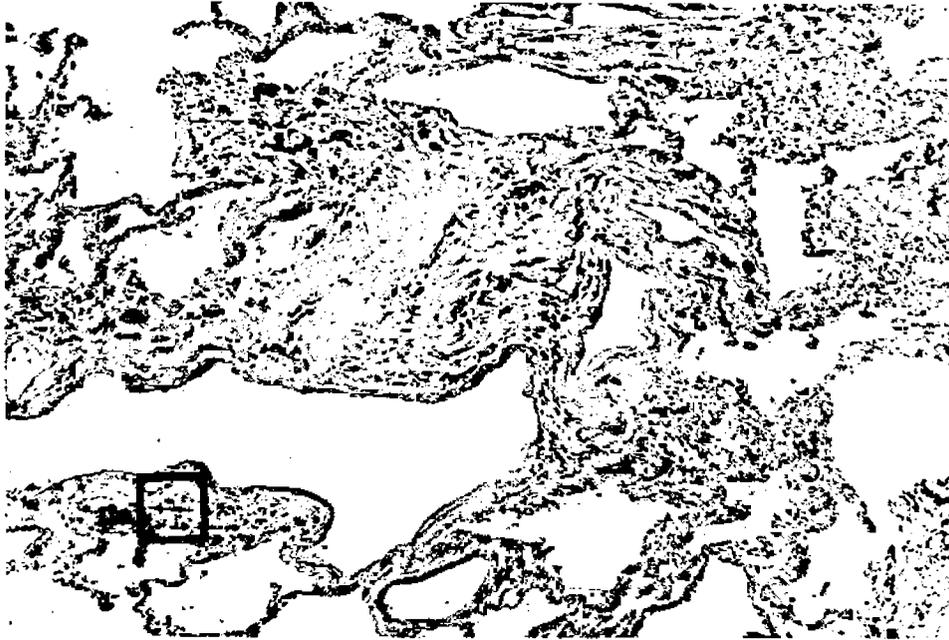


Figure II-14. Section of lung from 68-year-old asbestos insulation worker showing the histological features of mild asbestosis. The lesion is characterized by peribronchiolar fibrosis in which there are numerous asbestos bodies. Inset shows an asbestos body. Hematoxylin and eosin $\times 100$.

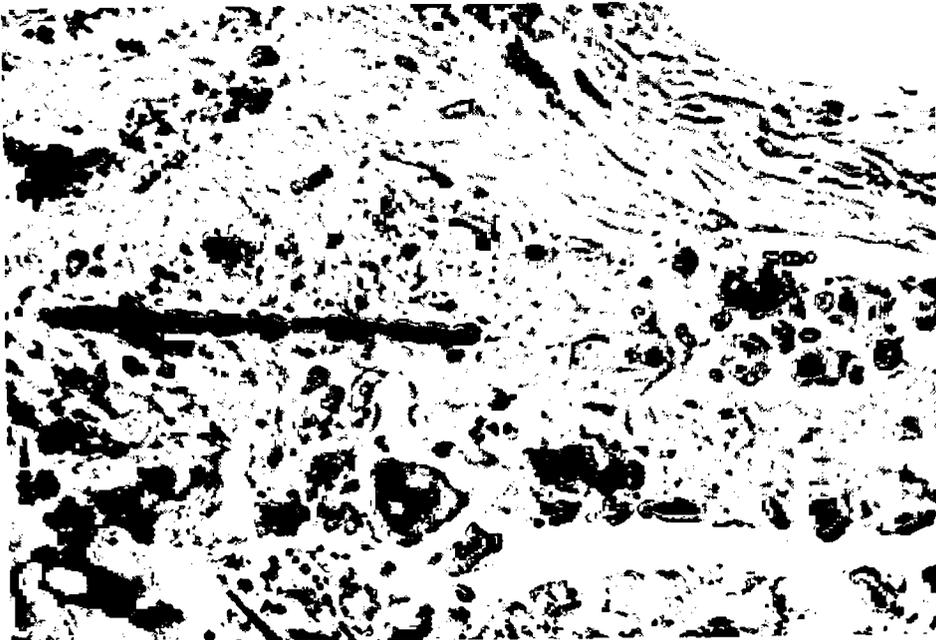


Figure II-14 (Inset).

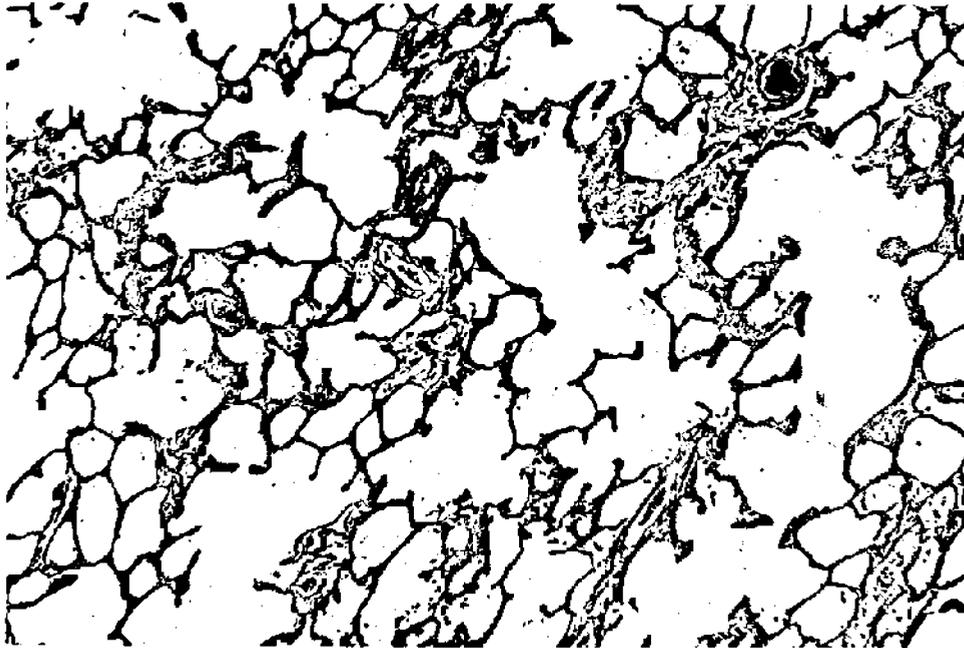


Figure II-15. Section of lung from 48-year-old worker in an asbestos textile mill showing diffuse interstitial and peribronchiolar fibrosis. Hematoxylin and eosin x 40.

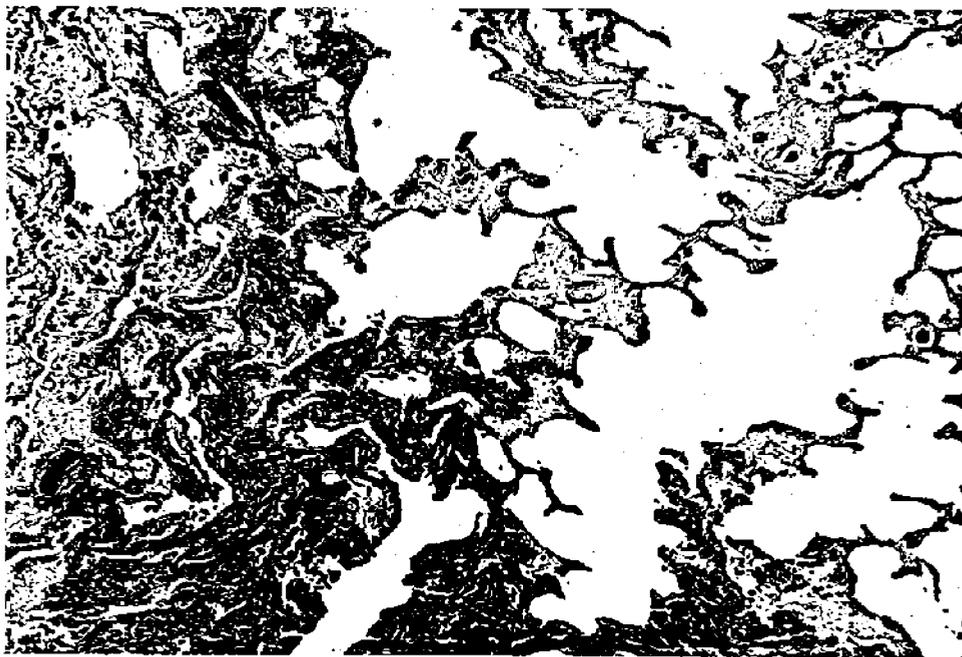


Figure II-16. Section of lung from same case as figure 15 showing interstitial and intraalveolar fibrosis. Hematoxylin and eosin x 40.

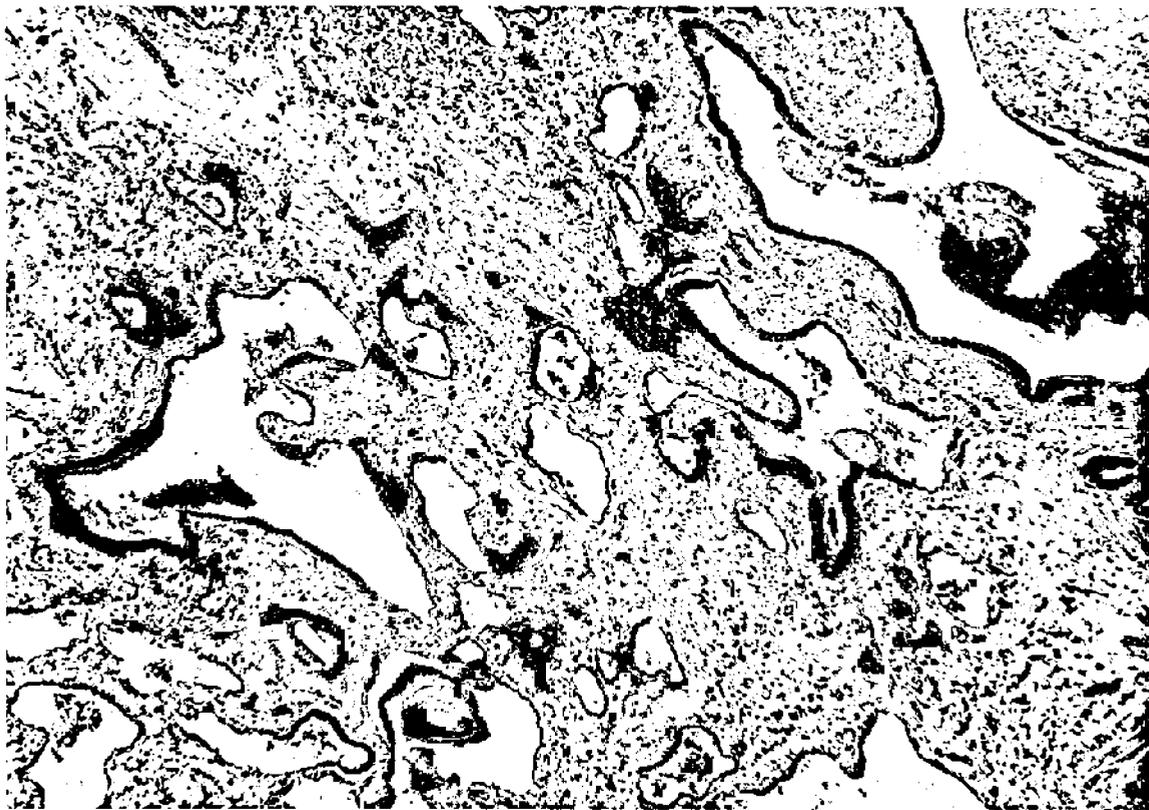


Figure II-17. Section of lung showing honeycombing. The pulmonary architecture has been replaced by thick bands of fibrous tissue outlining cystic spaces. There is a moderate chronic inflammatory cell infiltrate of the parenchyma. Hematoxylin and eosin \times 40.

showing a preponderance of adenocarcinomas.

Metaplastic and pre-malignant changes have been observed in the bronchi and within areas of fibrosis in asbestosis (42)(101). It has yet to be determined whether sputum cytology is of value in early detection of carcinoma in asbestos workers (35).

Mesothelioma

Mesothelioma is a rare tumor arising from the mesothelial cells that line the pleural, pericardial, and peritoneal cavities. The first case associated with asbestos exposure was reported by Wyers in 1946 (165). In 1960 this association was firmly established by Wagner and co-workers in a study of individuals exposed to crocidolite asbestos in the Northwest Province of South Africa (152). Since then, cases have been reported from all major industrial countries. Exposure to crocidolite and amosite (45) (125) appear to carry the greatest risk for developing mesothelioma, whereas workers exposed predominantly to chrysotile asbestos appear to have the least risk (18)

(45). The tumor is almost invariably associated with asbestos exposure—a positive history being obtained in 80-90% of cases (13)(151); however, there is no evidence for a dose-response relationship. Although exceedingly rare in the general population, mortality from mesothelioma may approach 10% among some groups of asbestos workers (127).

The tumor occurs in both sexes and has a latency period in excess of 20 years—usually 30 to 40 years. There is no association with cigarette smoking. The tumors are ivory colored and, in typical cases of pleural mesothelioma, encase the lungs in a rubbery mass of tissue. Pleural plaques and asbestosis may also be present, though in the majority of cases mesotheliomas occur in the absence of these lesions. The tumor tends to spread along the interlobar fissures and to invade the subpleural portions of the lungs. Direct invasion of adjacent organs, such as heart, diaphragm, and liver and extension into surgical incisions and aspiration needle tracts are characteristic. Metastases to local lymph nodes and the

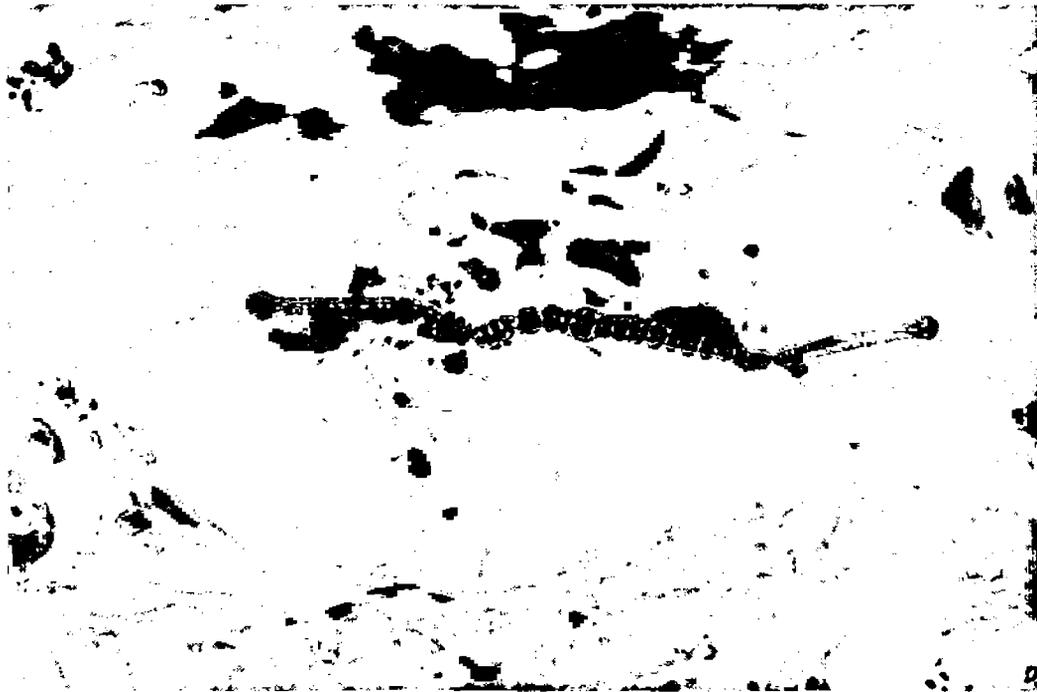


Figure II-18. Asbestos body within an area of fibrosis. The body is composed of a translucent core fiber with a beaded iron-protein coat. An uncoated fiber is also seen (arrow). Hematoxylin and eosin X 600.

lung are also fairly common. Extrathoracic metastases are relatively rare, and their presence should raise a suspicion as to the authenticity of the tumor.

Microscopically, the tumor can be classified into tubo-papillary, sarcomatous, and mixed types. The tubo-papillary is the most common type and is easily confused with metastatic carcinoma from the lung or elsewhere. Special stains may aid in differentiation in some cases. Mesotheliomas usually contain the mucopolysaccharide, hyaluronic acid, which stains with Hale's colloidal iron and with alcian blue. The specificity of the reaction can be determined by pretreatment of the tissue section with hyaluronidase (16). Hyaluronic acid may also be demonstrated by electrophoresis of tumor tissue (154). Adenocarcinomas usually contain intracytoplasmic mucin droplets rather than hyaluronic acid (16). More recently it has been suggested that the absence of carcinoembryonic antigen (CEA) may be a useful adjunct for diagnosis (153). In the United States and Canada, special panels of

pathologists (mesothelioma panels) exist to provide a diagnostic referral service (50).

CLINICAL EVALUATION

Clinical evaluation of the asbestos-exposed worker should include a full occupational and environmental history, full medical history, chest radiographs, and spirometry. Evaluation of the occupational and environmental history is especially important. The patient may have had only a few weeks of employment in construction or a shipyard as a summer job years before; yet, it is well documented that such brief exposures may manifest in asbestos related diseases 20 to 30 years later. It is important to assess other occupational exposures, such as coal or hard rock mining, which may produce rounded opacities on radiographic evaluation. Family history is also important. Asbestos insulation workers, as in many trades, tend to work in that trade from generation to generation. Therefore, the possibility of asbestos exposure in the home as a child should not be overlooked. Although a single PA radiograph is recommended for screening for

asbestos related disease in the clinical evaluation, a lateral chest radiograph should also be obtained to evaluate the lung zones behind the heart and provide a baseline for future evaluation. Although impairment is better correlated with radiographic abnormality in asbestosis than in other forms of pneumoconiosis, it is still highly variable. Therefore pulmonary function evaluation is required to assess the nature and extent of lung function abnormality.

Symptoms and Signs: Unlike silicosis and coal workers' pneumoconiosis, the asbestos worker may present with dyspnea in the absence of radiographic abnormality. Exertional dyspnea is the most prominent symptom with progression and is the major complaint in asbestosis. A chronic cough which is usually dry, but which may be productive especially among smokers and those working a dusty job, is another common finding. This is consistent with epidemiological studies showing increased bronchitis and airways obstruction especially among smoking asbestos workers. With progression of asbestosis, dyspnea becomes marked and is accompanied by tachypnea.

Pleural plaques or thickening are typically not accompanied by symptoms and may therefore be present years before detection. Some of these patients will report chest tightness or difficulty taking a deep breath. With marked pleural thickening, dyspnea is usually the principal complaint. Asbestos induced pleural effusions are not unusual and may cause pleuritic pain, but pleural pain is often not present even when a friction rub is heard.

Physical examination is usually not remarkable, especially in early cases of asbestosis. In most cases, the first sign, and often the only sign, is crisp basal crepitations usually best detected anteriorly and laterally at the end of a full inspiration. Clear mid-inspiratory crepitations may be heard over the mid and lower lung zones in more advanced cases of asbestosis. Digital clubbing is found in advanced asbestosis. Cyanosis, like clubbing, is a late sign in those with far advanced disease.

Physical findings in patients with pleural plaques or thickening are few unless the thickening is marked or an effusion is present. In such instances decreased thoracic expansion, dullness to percussion, and diminished breath sounds are found. Pleural friction rubs may also sometimes be detected in patients with pleural involvement.

Radiographic Findings: The radiographic findings of asbestosis and asbestos related pleural plaques and thickening are best described through systematic application of the 1980 ILO Classification for interpretation of the pneumoconioses (44). Guidelines for obtaining a technically satisfactory radiograph and for its interpretation are included in the 1980 ILO Classification. Because of the well known variation in interpretation of radiographs from reader to reader, it is recommended that the ILO standard films be used as a guide and that more than one independent reading be obtained (89). This is especially important in evaluation of clinical series and in population studies.

The small irregular opacities of asbestosis are most commonly distributed in the mid and lower lung zones. Their profusion (number of opacities per unit area) is dependent on the degree and length of asbestos exposure and may be quantified into categories (0,1,2,3, by the 1980 ILO Classification). The size and shape of the opacities may be described by using the symbols "s" (irregular opacities less than 1.5 mm in diameter), "t" (irregular opacities 1.5 to 3.0 mm in diameter), or "u" (irregular opacities greater than 3 mm, but less than 10 mm in diameter). Rounded opacities (p,q,r) may also be seen, but if profuse should alert the reader to the possibility of other siliceous dust exposure—this pattern is not uncommon among asbestos miners and asbestos cement manufacturers. With progression, all lung zones may be affected and radiological evidence of honeycombing in the lower zones is not unusual (Figure II-19). Rarely coalescence of opacities may produce large opacities which are ill defined and may be several centimeters in diameter (Figure II-20). Other late manifestations include irregular diaphragmatic, pleural and cardiac borders ("shaggy heart"), often associated with pleural thickening or plaques (Figure II-21).

It is, however, the early cases of asbestosis rather than the advanced cases which are difficult to interpret. It is known that smoking and repeated infections (bronchitis and pneumonia) may produce irregular opacities, especially in older individuals. Morgan et al. have shown that as a consequence, the frequency distributions of small opacities in persons with and without pneumoconiosis may be expected to overlap each other at a low profusion level (90). This obser-



*Figure 11-19. Advanced asbestosis—profusion 3/3 with all lung zones involved with s/t opacities.

*Source: American College of Radiology Teaching Module on Asbestos Related Disease. American College of Radiology, Chevy Chase, Maryland, 1981 NIOSH contract.

vation, together with reader variability, means that caution must be used in ascribing low levels of profusion (0/1,1/0) to asbestos exposure, without consideration of other factors or etiologies—scleroderma, lipoid pneumonia, desquamative interstitial pneumonitis, and sarcoid may all present with basal irregular opacities similar to asbestosis.

Pleural plaques are fibrotic processes which begin below the surfaces of the parietal pleura, are usually smooth or nodular, are often bilateral, and are rarely over 1 cm in thickness. They are most commonly found on the posterolateral or anterior chest walls between the sixth and tenth ribs and in the aponeurotic portion of the diaphragm. Pleural plaques tend to spare the apices and costophrenic angles and, with time, tend to calcify. Plaques vary from small circular or linear opacities to large irregular opacities—

some may encircle the lung. Even without calcification, they are sufficiently characteristic that an asbestos etiology should be presumed whenever they are seen. They greatly assist in the assessment of early parenchymal disease.

The 1980 ILO Classification provides an expanded and complete scheme for codifying pleural changes arising from asbestos exposure (44). The reader is asked to note whether the diaphragm and costophrenic angles are affected. Classification is provided for both diffuse and circumscribed plaques by width (O, A, B, C) and extent (0, 1, 2, 3) evaluated en face on projections. Finally, pleural calcification on the diaphragm, chest wall, or other sites may be specified.

Pleural plaques are often mimicked by the images of small divisions of the external abdominal oblique and the serratus anterior muscles which originate from the external surfaces of the



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*Figure 11-20. Advanced asbestosis—profusion 2/3 with all lung zones involved with s/t opacities. Large opacities in left mid-zone. Poorly differentiated squamous cell carcinoma of the right hilum.

*Source: American College of Radiology Teaching Module on Asbestos Related Disease. American College of Radiology, Chevy Chase, Maryland, 1981 NIOSH contract.

ribs posteriorly and laterally. Unlike most plaques, however, these images are bilaterally symmetrical, occur in rhythmic sequence along the lateral chest walls, are generally smooth, regular, and less opaque than plaques. Oblique radiographs are often useful in differentiating these shadows from plaques or to better define plaques.

Lung Function: Lung function testing has been applied to the study of asbestosis since its introduction to clinical medicine in the 1940's. The specific type of lung function test is dictated by the type of investigation. Spirometry has served well as a tool for industrial medical surveillance and for prospective epidemiological studies. Assessment of lung volumes and gas exchange (D_{LCO} and arterial blood gases) have been useful additional laboratory tests used to evaluate those exposed to asbestos.

Classically, advanced asbestosis has been considered as a disease which restricts lung volumes (especially VC, and to a lesser extent, RV) and produces gas exchange measurements consistent with an "alveolar capillary" block (i.e., decreased D_{LCO} and in more advanced cases, depressed resting Pa_{O_2})(3). CO_2 exchange is usually not affected. In far advanced cases arterial oxygen desaturation is observed; this usually corresponds to central cyanosis and marked dyspnea.

Recent papers on lung function among those with asbestosis have suggested that a mixed restrictive and obstructive pattern and obstructive defect are also commonly found among those with asbestosis. In 1972, Muldoon and Turner-Warwick reported 13 of 60 asbestos workers evaluated at the Brompton Hospital had a pure



***Figure II-21. Chronic calcified fibrous pleuritis involving the right chest wall and costophrenic angle.**

*Source: American College of Radiology Teaching Module on Asbestos Related Disease. American College of Radiology, Chevy Chase, Maryland, 1981 NIOSH contract.

obstructive ventilatory defect; 3, a mixed pattern; 32, restriction; and 12 were normal (72). In 1975, Fournier-Massey and Becklake reported that among 1,000 Canadian asbestos miners and millers, 12.8% had a restrictive pattern and 12.2% an obstructive pattern (30). Murphy et al. in a study of shipyard workers, found no more obstruction among asbestos workers than matched controls (94). However, Rodriguez-Roisen et al. recently reported an obstructive pattern, defined by reductions in forced expiratory flow at 75% of the vital capacity, in 34 of 40 asbestos workers referred to the Pneumoconiosis Medical Panel and the Brompton Hospital, London (114). Although only 7 of 34 were considered non-smokers, the authors suggest that airways obstruction, particularly affecting small airways, is a common functional abnormality attributable

to asbestos exposure. This view is consistent with pathological observations which show peribronchiolar fibrosis to be an early lesion in asbestosis (see Pathology). The extent and severity of obstructive defects among asbestos workers, however, still needs full epidemiological evaluation with attention to other risk factors, especially smoking.

Other Medical Tests: Serological tests of those with asbestosis have shown increased levels of antinuclear factor (ANF) and rheumatoid factor (RF)(142)(147). Others have reported normal levels in mild cases, suggesting that these findings may be the result of nonspecific lung damage (24)(144). However, Gregor et al. have recently reported a series of 119 subjects followed prospectively at the Brompton Hospital and assessed for progression in asbestosis relative to auto-

antibody status (36). Although the numbers were small, there was some suggestion that those who showed a progression over three to seven years had higher antinuclear antibody titers and with greater frequency. These authors suggest that this finding, if confirmed, might indicate a greater degree of inflammation associated with greater alveolar macrophage turnover; this may be an important event in rapid progression among some with asbestosis.

HLA phenotype is another serological test which has been studied in relationship to asbestosis, extent of radiographic profusion, and progression of asbestosis. In a preliminary study, Merchant et al. reported a slight increase in HLA-27 phenotype among men with asbestosis and this was associated with a greater degree of fibrosis (radiographic profusion) (82). However, upon prospective evaluation of the HLA system in asbestosis, Turner-Warwick concluded that HLA phenotype was not of significant importance in the etiology of asbestosis (146).

PREVENTION

Available epidemiologic data support a linear, no threshold dose-response relationship between asbestos exposure and the risk of lung cancer. Additionally, no threshold has been convincingly demonstrated for nonmalignant respiratory diseases associated with asbestos exposure. Thus, any asbestos exposure carries with it some increased risk of asbestos related diseases. Accordingly, asbestos exposure should be eliminated or reduced to the lowest level possible.

The most effective method for eliminating asbestos related diseases is substitution of less toxic materials or modification of a process or product to eliminate asbestosis. Materials commonly used for substitution include fibrous glass, rock wool, slag wool, and various ceramic and man-made fibers. Asbestos pipe insulation has been satisfactorily replaced with calcium-silicate insulation block. These substitute materials are not totally without risk; thus appropriate work practices and engineering controls are still required.

Appropriately designed and maintained engineering techniques are the control method of choice where asbestos substitutes cannot be used. Processing of asbestos in a wet state has been shown to be an effective control method in many asbestos processing industries, includ-

ing the asbestos textile industry. The most commonly used control measure in asbestos processing plants is local exhaust ventilation whereby liberated dust is collected at the dust source and removed from the breathing zone of workers. Methods of local exhaust ventilation also have been developed for handtools such as saws and drills used in the construction industry.

Appropriate work practices are an important component of any dust control program. These include use of wet methods or high efficiency vacuum cleaners for cleaning of asbestos contaminated areas and proper disposal of asbestos contaminated waste. Showering and changing of work clothes at the end of the work shift are important in eliminating "take-home" exposures. Respiratory protection is appropriate for short-term jobs or operations where controls may be unfeasible; however, use of respirators is not an acceptable substitute for engineering controls.

The combined effects of asbestos exposure and cigarette smoking in increasing the risks of lung cancer and asbestosis are well established. In addition to reducing or eliminating asbestos exposures, asbestos workers should be educated on the multiplicative risks of smoking and asbestos exposures and encouraged not to smoke. Anti-smoking programs are important for asbestos workers.

Various regulations have been promulgated in the United States specifying exposure limits, exposure monitoring requirements and medical surveillance requirements. In 1972, the Occupational Safety and Health Administration promulgated its first exposure standard for asbestos fibers, specifying a limit of five fibers/cc of fibers longer than $5\mu\text{m}$ (fibers/cc) on an eight hour time-weighted-average basis. This was reduced to two fibers/cc on July 1, 1976. Subsequent reviews of new literature on health hazards of asbestos prompted the National Institute for Occupational Safety and Health to recommend an eight hour exposure limit of 0.1 fiber/cc and elimination of all but essential uses of asbestos.

Research Priorities: Although asbestosis is well characterized clinically and has been the subject of a good deal of epidemiological research, a number of research priorities remain:

1. Epidemiological studies are needed to further characterize: potential asbestos risk from exposure in the railroad in-

dustry; tremolite exposure from contaminated vermiculite and talc in the users of these products; the risk (if any) among those working in the crushed stone industry; and to assess the risk of pleural abnormalities in the absence of parenchymal changes.

2. Research is needed to further assess differences in lung cancer and pneumoconiosis risks for various manufacturing and mining populations.
3. Pathological standards developed to characterize asbestosis need to be tested for reliability and validity in a controlled trial.
4. More sensitive and specific tests are needed to assess asbestos lung deposition and injury.
5. Immunological, serological, and bronchial lavage studies of the progression of asbestosis are needed to better characterize the natural history of asbestosis.
6. Experimental animal and clinical trials with promising chemotherapeutic modalities, for both asbestosis and asbestos associated cancer, should be a high priority.
7. Research must continue on other fibrous materials, such as wollastonite and fine fibrous glass and mineral wool, to document other health effects which may be associated with these fibrous materials.

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COAL WORKERS' PNEUMOCONIOSIS AND EXPOSURE TO OTHER CARBONACEOUS DUSTS

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INTRODUCTION

Historical accounts of "Miners' Black Lung" date to 1831. Since that time, numerous clinical and epidemiological studies have documented the existence of Coal Workers' Pneumoconiosis (CWP) and associated lung impairment among miners. Extensive British prospective studies have established dose-response relationships between CWP and respirable coal mine dust. The Federal Coal Mine Health and Safety Act of 1969 (P.L. 91-173) established a coal mine dust standard (based upon the British data); mandated provisions for other safety and health standards; provided health surveillance, transfer rights, and rate retention for miners; provided federal compensation for "Black Lung"; and guaranteed NIOSH right of entry for further research in coal mining. In many ways, this Act served as a model for subsequent legislation and health standards from other exposures (see Table II-13).

Because of the importance of coal as an energy source, and because of our vast coal resources, coal dust and coal products (synfuels) will continue to be produced for decades to come (see Figure II-22 and Tables II-14 and II-15). Graphite and carbon black represent other important carbonaceous exposures found in dozens of commercial processes in several industries; these exposures will also continue and expand in the years to come. Therefore it is essential to understand the biological effects of these exposures and how these effects may be mitigated or prevented.

DEFINITION

In discussing coal workers' pneumoconiosis or pneumoconiosis arising from carbon dust exposure, it is essential to define pneumoconiosis and the popular term "Black Lung." Coal work-

ers' pneumoconiosis (CWP) and carbon pneumoconiosis are specific diseases resulting from the inhalation and deposition in the lung of carbonaceous dust and the lung's reaction to the dust so deposited. In CWP, the disease is manifest characteristically by the coal macule and later by coal micronodules and nodules resulting in simple coal workers' pneumoconiosis. In some cases large (1-3 cm) lesions, or even massive consolidated lesions, develop resulting in progressive massive fibrosis (PMF).

"Black Lung" is a legislatively defined term which encompasses the classical medical definition of coal workers' pneumoconiosis, but is defined by the Act as "a chronic dust disease of the lung arising out of employment in an underground coal mine." (Title IV—Black Lung Benefits—Part A—Federal Mine Safety and Health Act of 1977, P.L. 91-173 as amended by P.L. 95-164). This definition is used to cover disability primarily from chronic airways obstruction which is associated with coal mine dust exposure. Tuberculosis *per se* appearing in a coal miner has not qualified for benefits, nor has the development of other bacterial or viral illnesses, or lung cancer. In practice, however, miners with these and other chronic lung conditions who meet any of the qualifying criteria in the Act—if in the judgment of the examining physician and administrative law judge they have developed their condition in association with coal mine employment—may be compensated for total disability. Medical costs for these conditions have been paid by the Department of Labor. Thus the definition of "Black Lung" is broad and imprecise; it will not be discussed further in this chapter.

Table II-13
COAL MINING HEALTH AND SAFETY
LEGISLATION IN THE UNITED STATES*

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|--|---|
| <p>1865: Bill is introduced to create "Federal Mining Bureau." It is not passed.</p> <p>1910: Bureau of Mines is established, but specifically denied right of inspection.</p> <p>1941: Bureau of Mines is granted authority to inspect, but it is not given authority to establish or enforce safety codes (Title I Federal Coal Mine Safety Act).</p> <p>1946: Federal Mine Safety Code for Bituminous Coal and Lignite Mines is issued by the Director, Bureau of Mines (agreement between Secretary of the Interior and the United Mine Workers of America) and included in the 1946 (Krug-Lewis) UMWA Wage Agreement.</p> <p>1947: Congress requests coal mine operators and state agencies to report compliance with the Federal Mine Safety Code. Thirty-three percent compliance is reported.</p> <p>1952: Title II of the Federal Coal Mine Safety Act is passed. All mines employing 15 or more persons underground must comply with the Act. Enforcement is limited to issuing orders of withdrawal for imminent danger or for failure to abate violations within a reasonable time.</p> <p>1966: Amendments to 1952 law. Mines employing under 15 employees are included under 1952 Act; stronger regulatory powers are given to Bureau of Mines, such as the provision permitting the closing of a mine or section of a mine because of an unwarrantable failure to correct a dangerous condition.</p> <p>1969: Federal Coal Mine Health and Safety Act is passed. In this Act the hazards of</p> | <p>pneumoconiosis are, for the first time, given prominence, in addition to those of accidents.</p> <p>1972: Black Lung Benefits Act of 1972 is passed. Several sections of Title IV are amended, liberalizing awarding of compensation benefits.</p> <p>1977: Federal Mine Safety and Health Act of 1977 is passed. This Act amends Coal Mine Health and Safety Act of 1969 largely by adding health and safety standard setting, inspection, and research provisions for metal and nonmetal miners while leaving the 1969 Act largely intact. This Act also consolidated health and safety compliance activities for general industry (OSHA) and mining (MSHA) in the Department of Labor.</p> <p>1977: Black Lung Benefits Revenue Act of 1977 was passed. This provided for an excise tax on the sale of coal by the producer to establish trust funds to pay black lung benefits.</p> <p>1977: Black Lung Benefits Reform Act of 1977 was passed. This Act was passed to improve and further define provisions for awarding black lung benefits. Additionally, it established (a mandate) that a detailed study of occupational lung disease would be undertaken by the Department of Labor and NIOSH.</p> <p>1981: Black Lung Benefits Revenue Act of 1981 was passed. This Act was passed to increase revenue for the Black Lung Disability Trust Fund, based on a new tax on coal with respect to sales after December 31, 1981.</p> |
|--|---|
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*Source: (91)

Table II-14
U.S. COAL RESERVES

Coal Type	Short Tons
Bituminous	747,357 x 10 ⁶
Sub-Bituminous	485,766 x 10 ⁶
Lignite	478,134 x 10 ⁶
Anthracite	19,662 x 10 ⁶
Total	1,730,919,000,000

Source: (164)

Table II-15
U.S. COAL PRODUCTION FOR 1979
BY COAL RANK AND TYPE OF MINING

ANTHRACITE	
<i>Source</i>	<i>Short Tons</i>
Strip Mine	2,962,000
Deep Mine	595,000
Culm Bank (Anthracite waste)	1,480,000
Total	5,037,000
BITUMINOUS, SUB-BITUMINOUS AND LIGNITE	
<i>Source</i>	<i>Short Tons</i>
Strip Mine	462,324,000
Deep Mine	306,344,000
Total	768,668,000
*DOE Data	

Source: (81)

Table II-16
POPULATION AT RISK TO EXPOSURE
TO U.S. COALS
BY PRINCIPAL WORK AREA

Work Area	Anthracite	Bituminous & Lignite
Underground Miners*	483	141,065
Surface Miners	1,625	69,214
Preparation Plant	1,116	22,235
Shop	80	2,729
Totals	3,304	235,243

*Includes Mine Construction

Source: Personal Communication HSCAC, MSHA,
Denver Federal Center, February 19, 1981.

OCCUPATIONS AND INDUSTRIES INVOLVED

Within coal mining, exposure is commonly divided into underground and surface operations. Coal mine construction is included legislatively, and properly so, as an underground mining exposure (see Table II-16). Although most underground jobs result in heavier exposures to coal mine dust, certain surface jobs, particularly drillers, may have significant exposure to respirable coal dust and free silica.

Carbon black has been defined by the American Society for Testing and Materials as "a material consisting of elemental carbon in the form of near-spherical colloidal particles and coalesced particle aggregates of colloidal size, obtained from partial combustion or thermal decomposition of hydrocarbons." Carbon black is classified as furnace, thermal, or channel black depending on the manufacturing process (see Table II-17) (3).

As of 1976 there were eight companies operating 32 carbon black plants in the United States. Of the 2,924 million pounds sold domestically, 2,720 million were used in pigmenting and reinforcing rubber, 80 million in inks, 19 million in paints, and 3 million in the manufacture of paper. The remaining 102 million pounds were used in plastics, ceramics, foods, chemicals, and other products. The worker may be exposed during any of a number of processes including production, pelletizing, screening, packaging, loading, and unloading (130).

Graphite is widely used in a number of industrial applications and is the third major form of carbonaceous dust exposure (see Table II-18). Graphite may be natural graphite, also called plumbago, or artificial or synthetic graphite. The difference is important from a respiratory disease standpoint in that natural graphite, which is mined from siliceous sediments (Sri Lanka, Madagascar, Italy, Brazil) may contain significant percentages of free silica (11% in Italian graphite) (138). Synthetic graphite contains only traces of free silica except for pyrolytic graphite which may contain significant amounts of quartz and cristobalite (137).

ESTIMATE OF POPULATION AT RISK AND DISEASE PREVALENCE

Because of the extensive regulatory and health surveillance systems mandated by the Federal Coal Mine Health and Safety Act of

Coal Deposits in the United States

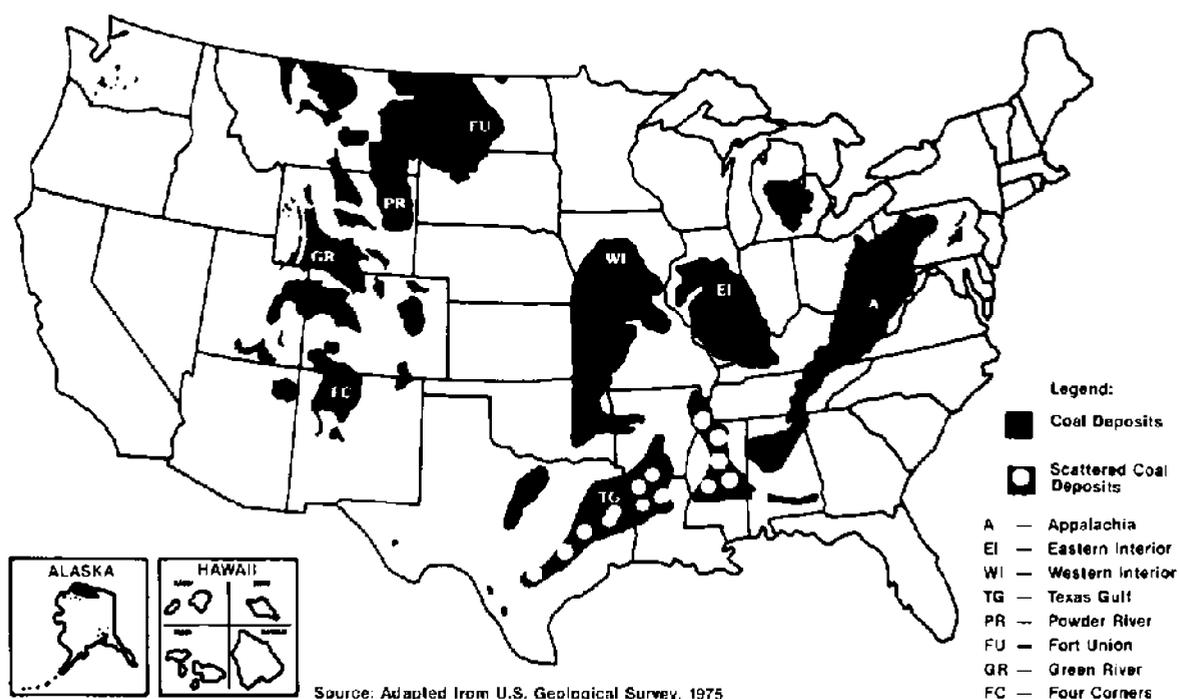


Figure II-22. Map of coal deposits.

1969, reasonably good estimates may be made in regard to underground coal miners. Table II-16 provides the most recent available figures on coal mining employment by type of coal mine and by type of coal. Estimates on the prevalence of CWP *per se* are provided from results of the third round of the NIOSH National Coal Workers' Health Surveillance Program (Table II-24). Similar estimates of CWP prevalence are not available for surface miners, as the Act did not mandate medical examinations for these miners and they are not yet covered by the health standard provision of the Act.

NIOSH estimates that approximately 2.4 million workers are potentially exposed to natural and synthetic graphites. Although pneumoconiosis, both simple CWP and PMF, is well documented in natural graphite workers and cited among synthetic graphite workers, the lack of epidemiological studies prevents making prevalence estimates.

NIOSH has estimated that 35,000 workers are exposed to carbon black directly or indirectly (130). There are only limited epidemiological

studies available, making any estimate of carbon pneumoconiosis in these industries impossible.

EPIDEMIOLOGY

The epidemiological literature on coal mining is vast and represents, for the most part, the best epidemiology has to offer in defining occupational disease causality. Early observations were largely anecdotal but useful statistics were collected by about 1900. Since then, cohort mortality, cross-sectional, prospective and population based intervention studies have greatly expanded our understanding of the health effects of coal mine dust exposure. However, gaps remain in our understanding of certain aspects of coal dust induced diseases and in the quantitation and interaction of risk factors.

Historical Perspective

The three part series entitled "History of Lung Diseases of Coal Miners in Great Britain" published in 1951-52 by Andrew Meikeljohn provides an excellent review of the evolution of observations on coal workers' pneumoconiosis between 1800 and 1950 (109-111). Historical

Table II-17
PHYSICAL AND CHEMICAL PROPERTIES
OF VARIOUS TYPES OF CARBON BLACK

Property	Furnace Black		Channel Black	Thermal Black
	Oil	Gas		
Composition				
Carbon (%)	98	99.2	88.4-95.2 (Avg. 91.2)	—
Oxygen (%)	0.8	0.4	3.6-11.2 (Avg. 7.8)	—
Hydrogen (%)	0.3	0.3	0.4-0.8 (Avg. 0.6)	—
Ash-Ca, Mg, Na (%)	0.1-1.0	0.1-1.0	0.01	—
Volatile matter (%)	1-2	1-2	5-18	1
Average particle diameter (μm)	0.018-0.06	0.04-0.08		0.01-0.03
0.14-0.47				
Specific surface (Sq. mg/g)	25-200	25-50	100-1,000	7-13
pH	8-9	8-9	3-5	8-9
Benzene extractables (%)	0.05-0.1	0.05-0.15		—
0.03-1.75				

Source: (130)

Table II-18
OCCUPATIONAL EXPOSURES
TO NATURAL GRAPHITE

Refractory ceramics and crucibles Foundry facings Steel and cast iron manufacture Pencils Lubricants Neutron moderators in atomic reactors Electrodes Electrotyping Graphite mining and milling

Source: (137)

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accounts often provide the most lucid descriptions of diseases and reveal insights into the pathogenesis and prevention of diseases that are often held to be recent advances. Such is the history of coal workers' pneumoconiosis.

Although coal was mined from outcroppings by the workers of Newbattle Abbey as early

as 1291, significant occupational exposure to coal mine dust did not occur until after the invention of the steam engine which was first applied to underground mining in Scotland in 1762. By 1839, it was estimated that Britain was producing 36,000,000 tons of coal, and by 1866 over 100,000,000 tons were being mined by a work force of over 320,000 (109).

The first report of the Commissioners on Children's Employment in Mines (H.M.S.O., 1842) provides an early account of working conditions in coal mines. Employment was not confined to men but also included women and children. Ventilation was reportedly so poor and the air so thick with carbonic acid gas, gunpowder fumes, and smoke from oil lamps and tallow candles, that it was often inadequate to sustain hard labor or the lamps (109).

French pathological anatomists Bayle and Laennec described "melanosis" but did not associate these dark blue or black lungs with occupation (109). Pearson wrote the first English

Table II-19
OCCUPATIONS WITH POTENTIAL
EXPOSURE TO CARBON BLACK

Battery workers
Carbon black workers
Carbon electrode workers
Carburization workers
Cement workers
Ceramics workers
Food processors
Ink workers
Paint manufacture workers
Paper workers
Plastic workers
Printers
Rubber workers

Source: (130)

paper on "melanosis" and linked it with the living environment (109). In one case, he further attributed this condition to tobacco smoking.

In 1831, Gregory published a "Case of Peculiar Black Infiltration of the Lungs Resembling Melanosis" based on his pathological observations on a 59-year-old collier (a coal miner) who died of progressive heart failure—the first case reported to arise from coal mine employment. He observed that this black infiltration differed from melanosis; was similar to a "form of phthisis" prevalent among "stone cutters, millers, and needle-grinders," and that it was possibly due to the inhalation of coal dust (109).

Among the clearest early descriptions of the pulmonary pathology found among colliers are those of Dr. William Craig of Glasgow. He clearly appreciated the importance of studying lungs fixed in inflation allowing assessment of dust deposition and emphysema (32):

It is only in the case of colliers, molders, or others who make large quantities of black matter, that the lungs are reduced perfectly solid. The best manner of ascertaining the exact situation of the black matter in such cases is by inflating the lung slightly, drying it thoroughly, and then cutting it into slices in various directions. Where the lung is prepared in this manner, the air cells can be distinctly seen with the naked eye, and by means of a small magnifier the exact situation of the black matter may be easily ascertained.

The "Black Infiltration" was first described as "anthracosis" by Dr. Thomas Stratton in 1837, preceding by nearly thirty years Zenker's generic "pneumoconiosis" (159). Considerable clinical interest in this condition is evident from several accounts dating to this period. W. Thomson provides the following account of the clinical picture with advanced disease (161):

He has a considerable degree of the stoop or rounded curvature of the back which is so frequently seen in old asthmatics, and his sternum and ribs are projected forwards in the manner in which they are usually seen to be in such individuals.

Pathological studies by Thomson and others described two types of "black infiltration" which closely approximate our current understanding of simple coal workers' pneumoconiosis and progressive massive fibrosis. Pneumoconiosis arising from working with stone as opposed to coal was recognized to be of different etiology and significance (109).

By 1851, the etiology and importance of respiratory disease among colliers was well enough established that physicians were calling for preventive measures in the mines. William Calder concluded his Edinburgh Clinical Club presentation with the following admonition (14):

The disease, once established, does not admit of cure or art. The only means of preventing the disease seems to consist of ventilating the mines where colliers work, or adapting a means of carrying off the fumes to which the moulders of iron and copper are exposed. Such prophylactic measures are equally called for, whatever theory of the nature of the disorder shall ultimately prove to be correct.

J. B. Thomson (1858) further observed (106):

I cannot help thinking that medical inspectors should, long ere this, have been appointed to cooperate with mining engineers, in order to apply the most enlightened rules of hygiene for the safety and health of this numerous and important class of work people. Had this been the case, I am satisfied that the true cause or causes of their diseases would, ere now, have been much palliated or prevented.

In 1860 and 1861, Dr. Greenhow was assigned from the Privy Council to inquire into the excessive mortality among colliers from respiratory diseases (50). Greenhow, who made other important observations on bronchitis and respiratory disease among cotton textile workers, com-

mented on the "asthmatical symptoms" leading many to be "disabled at from 40 to 50 years of age." This is perhaps the earliest observation of the importance of airways disease among coal miners.

By 1871, there was clear evidence that steps were being taken to adequately ventilate the coal pits. Mr. Leonard Brough, H. M. Inspector of Mines for South Wales and Monmouth commented (12):

Abundant ventilatory power, plenty of room for air in motion throughout the pit, attention to the state of the atmosphere, good officers and strict discipline; these are the arcana of safety underground, if indeed there are any secrets in the matter, which I very much doubt, for it is only a question of money after all.

Apart from ventilation, the importance of transferring affected miners out of dusty areas appears to have been appreciated as early as 1875. Therefore, the basic elements of a prevention program for respiratory disease among coal miners had been established more than a century ago.

In 1880, the first Workmen's Compensation Act was passed in Britain to provide compensation for accidents during employment. It was not, however, until 1904 that the first occupational disease, lead poisoning in pottery workers, was compensated (110). With better ventilation and shorter working hours, serious respiratory disease among coal miners appeared to decline markedly. This was supported by available Registrar-General data between 1871-1880. Based on this data and clinical observation, it was concluded that coal miner mortality only slightly exceeded that of a number of "healthy classes of men." Attention turned to silica exposure among cutlery grinders, earthenware workers, stone masons, and sandstone quarrymen with special attention to the importance of silica exposure and the risk from tuberculosis. Coal dust exposure, it was suggested, perhaps even retarded the development of tuberculosis (63). Still, it was appreciated that coal miners suffered more respiratory diseases than most other industries. Arlidge, in his text "The Diseases of Occupations," commented on the multiple causes for dyspnea among miners—deposition and "infarction" of the lung with "foreign matter," "bronchial trouble. . . with its attendant plugging with mucous and thickening of the lining membranes of the tubes;" ". . . the greater or less extent of tissue in an emphysem-

atous state;" and "cardiac disease secondary to the respiratory disease" (4).

By 1906 a Departmental Committee on Compensation for Industrial Diseases was established to determine which diseases should be scheduled as occupational in nature, and despite conflicting testimony, found (110):

We are clearly of the opinion that coal miners are not liable to fibroid phthisis, and although cases of anthracosis, using the term to mean cases in which the lung is charged with coal dust, are commonly met with, we cannot find that in any one that condition has proved to be a contributory cause of death.

This finding was reinforced by E. L. Collis in his 1915 Milroy Lectures on industrial pneumoconiosis (26):

I have attempted to justify the claim that dust inhalation plays an important part in determining the occurrence of respiratory diseases. Some dusts such as coal, it is true, not only appear to have no power of producing pneumoconiosis, but even may possess some inhibitory influence on phthisis; but most dusts have an injurious influence, and of all dusts that of silica is most injurious.

However, thirteen years later Collis and Gilchrist published an important paper, "Effects of Dust upon Coal Trimmers," in which the mortality experience of Welsh coal trimmers was compared to all males in England and Wales (27). The low rate of "phthisis" was again noted, but only among younger miners—what today we would suspect to be a "healthy worker effect." Unusually high mortality was, however, observed for bronchitis and pneumonia. Further, chest radiographs, then only recently applied to the study of respiratory diseases, demonstrated radiographic changes previously widely regarded as only characteristic of silicosis. Because none of these men had previous occupational exposure to silica, this paper provided the basis for establishment of coal dust as a separate cause of pneumoconiosis. Also in 1928, coal miners were first included in the Various Industries (Silicosis) Scheme (established in 1919), but only coal miners thought to have also had silica rock dust exposure (11).

Among the many pursuits of the famous physiologist T. S. Haldane, was an interest in mining and respiratory diseases of miners. Haldane, in addition to his post as professor of physiology at Oxford, was honorary director of the Mining Research Laboratory in Birmingham. He

was largely responsible for the introduction of rock dusting as a means to prevent explosions. He also held strong views on the nature of respiratory disease among coal miners and strongly opposed the inclusion of coal miners' compensation for silicosis. He recognized that the radiographic appearance of "coal miners' pneumoconiosis" was indistinguishable from that of silicosis, but opposed making a diagnosis without benefit of occupational history. He was also convinced, prophetically it would appear today, that bronchitis among coal miners was a major source of their respiratory disease. In regard to bronchitis and dust exposure he stated that "it seemed practically certain that excessive inhalation of coal-dust or shale-dust must cause bronchitis and ought therefore to be avoided (111)."

The Various Industries (Silicosis) Scheme of 1928 was amended and extended in 1931 and again in 1934, to include all underground colliery workers. "Silicosis" claims among miners in South Wales increased markedly, yet many cases thought to be atypical were refused (111). As a result there was a public demand for scientific investigation which was begun in 1936 when the Medical Research Council was asked by the Home Office and the Mines Department to investigate chronic respiratory disease among coal miners, especially those in South Wales. Medical Research Council (MRC) Reports were issued in 1942, 1943, and 1945 (108). The findings reported by Hart and Aslett confirmed the importance of free silica exposure in the causation of classical silicosis, but found that the vast majority of pneumoconiosis cases arose from coal mine dust exposure—especially among those at the face, but also among others working underground, among those "screening" coal on the surface, and among coal trimmers. As a result of these studies, and the growing social and economic problems faced by coal miners, the Coal Mining Industry Pneumoconiosis (Compensation) Scheme was passed and became effective July 1, 1943 (111). In order to deal with questions raised about the treatment and rehabilitation of coal miners, the Minister of Fuel and Power appointed a committee which published a report one year later (114). Two important recommendations were to establish: 1) a rehabilitation and treatment (clinical) research center, and 2) facilities for pathological research into dust deposition and disease. The MRC Pneumo-

coniosis Research Unit was established under the direction of Dr. Charles M. Fletcher, in 1945.

Mortality Studies

The earliest reliable mortality data on coal miners date to the 1906 British Registrar General occupational mortality statistics for the years 1890-2 and 1900-2. These figures suggested that overall coal miner mortality was declining, a view consistent with the predominant clinical view that respiratory disease among miners was decreasing. However, in 1928, Collis and Gilchrist reported that coal trimmers, who were not exposed to the free silica encountered in mining, clearly had pneumoconiosis (27).

Cancer Mortality: Early mortality studies of miners concentrated on cancer mortality. This was the result of a follow-up to a study of cancer of the bladder and prostate in various occupational groups, by Kennaway and Kennaway. Their initial study focused on coal miner mortality from cancer of the larynx and lungs in England and Wales from 1921-32 (80). Low ratios of observed to expected deaths were observed for all airway categories. A later study by the same authors (79) suggested that miners with high rates of pneumoconiosis had low rates of lung cancer and vice versa. In order to test this reciprocal hypothesis, James (76) studied 1,827 coal miners with pneumoconiosis and 1,531 noncoal workers in South Wales. Miners with slight pneumoconiosis were found to have a lung cancer ratio similar to non-coal workers; however, with progressively more severe simple CWP and especially within PMF, cancer rates fell. This suggested to James that early death from pneumoconiosis was likely a factor in the reduction of cancer deaths among coal miners. Interest in the possible associations between coal mining and lung cancer was continued by the 1958 study of Doll, who also found reduced lung cancer mortality among coal miners in four South Wales Districts (35). Based upon Registrar General data, Goldman calculated SMR's for miners and ex-miners; again underground miners were found to have low lung cancer SMR's compared to SMR's for surface miners and for other cancers. Goldman, however, found that coal mining towns generally also had lower lung cancer rates (46). Liddell, then with the National Coal Board, also reported reduced SMR's for lung cancer, particularly for underground workers—it was, however, noted that

there were not reciprocal increases in neoplasms from other sites (94). Recently Jacobsen and Miller et al. have reported on large mortality studies of British miners and have found no evidence of an association between lung cancer and coal mine dust exposure, nor was there any evidence that miners with CWP were at increased risk (39) (115).

It wasn't until 1963 that similar mortality studies began in the United States. Contrary to earlier British observations, Enterline reported an excess of lung cancer for his coal miner cohort (SMR = 192) (38). In a later paper, in which data from the Society of Actuaries over the periods 1915-26 and 1927-35 were analyzed, Enterline reported an overall greater than twofold excess mortality for coal miners, but a slight decrease in cancer mortality (SMR = 80) (39). A later U.S. Public Health Service mortality study of 3,726 miners who had participated in the 1962-63 Public Health Service coal miner prevalence study, revealed a total of only 30 lung cancer deaths and an SMR of 67 (29). The authors concluded that Appalachian miners appeared to have lung cancer mortality rates similar to those in Great Britain.

The most extensive mortality study of U.S. coal miners was recently completed by Rockette (150). He studied a cohort of 22,998 miners who represented a 10% sample of members of the United Mine Workers of America Health and Retirement Fund. The cohort was defined as of January 1, 1959, and consisted of all those eligible for benefits in the sample. Major findings are presented in Table II-21. Although the overall SMR (101.6) did not deviate significantly from 100, it is somewhat greater than that expected in a healthy working population. As a group, chronic respiratory diseases (influenza, emphysema, asthma, and tuberculosis) were significantly increased. Although bronchitis was not increased, it was noted that all deaths attributed to chronic bronchitis also mentioned emphysema on the death certificate. Other non-malignant respiratory diseases were significantly increased and account for the excess SMR under "all other causes" in Table II-21. Accidents also resulted in a significant excess of deaths—most accounted for by mine accidents. *Ill-defined causes* were also significantly increased, a finding attributed by the author as possibly being due to the rural nature of the cohort. Major cardiovascular dis-

ease accounted for the largest proportion of deaths but resulted in fewer deaths than expected. Hypertensive heart disease and hypertension were the only categories with SMR's over 100; the latter was found to be significant when compared to 1965 U.S. white male mortality figures. The author urged caution in accepting this because of the racial composition of the cohort.

Malignant neoplasms accounted for the second greatest proportion of deaths, but the SMR for all malignant neoplasms did not deviate significantly from 100. Analysis by neoplasm site, relative to the 1965 total male population, revealed a modest increase in stomach cancer with a reciprocal decrease in colon cancer. Respiratory cancer, particularly lung cancer, was also slightly increased, while cancer of the genital organs was decreased. The modest, but significant increase in lung cancer was noted by the authors to be well within the variation in SMR expected by regional or smoking differences (smoking histories were not available) between the cohort and control groups.

Alternatively, the excess in stomach cancer is consistent with that of other investigators, most of whom have found moderate yet significant excesses (33)(75)(103)(158). Because stomach cancer may be related to diet, ethnic origin, and socioeconomic class as well as environmental factors, Matalo controlled for these factors in studying two Utah counties where coal is both mined and burned in the home and another Utah county where the population is similar but where coal was not mined or burned (103). Pronounced increases in stomach cancer mortality, especially among men, was observed in the coal county—a finding the authors concluded could in part be related to "coal carrying carcinogenic hydrocarbons." A subsequent study of gastric cancer mortality in 23 coal producing counties with control counties matched by socioeconomic indicators, also reported excess risk ratios for stomach cancer (33). These investigators, based on other cancer risk ratios which corresponded to patterns previously associated with socioeconomic class, concluded that the increase in gastric cancer was a likely reflection of socioeconomic class, even though the exposed and control groups were well matched for education and income. However, recent British evidence has suggested a dust relationship with gastrointestinal cancer and pneumoconiosis (75) (115).

Pneumoconiosis Mortality: Mortality studies have been more consistent and definitive in resolving other questions about coal miner mortality. Although most mortality studies have revealed increased SMR's for respiratory diseases and it was clear that much of this excess was due to pneumoconiosis, it was not clear as to whether simple pneumoconiosis *per se* resulted in increased mortality nor what other risk factors may have influenced mortality rates. Beginning with the studies of Carpenter et al. in 1956 (16), miners' mortality was studied in relation to the ILO radiographic classification of pneumoconiosis* (69). Carpenter found minimal increases in SMR when comparing Category O or Category 1, 2, 3, simple CWP, and Category A of PMF with non-miners. However, this was not true of more advanced PMF, which appeared to be associated with increased mortality. Cochrane, in 1964, and again in 1973 (20 year follow-up of miners of the Rhondda Fach, South Wales) confirmed that Category O miners had an SMR similar to those with Category 1, 2, 3, and A radiographs while those with Category B, C, and D had a marked increase in mortality (22). The mortality of Category O miners was, however, somewhat less favorable than for controls. Similar observations were made by Ortmeyer who studied both anthracite and bituminous miners (135). SMR's for simple CWP and Category A PMF were not increased among bituminous miners but were somewhat increased in anthracite miners. Other categories of PMF were clearly increased in SMR. However, a recent report from the Institute of Occupational Medicine in Edinburgh based on a National Coal Board cohort has now reported decreased survival for miners with Category 1 simple CWP (see Table II-20) (115). This is a new and—because of the size and length of follow-up of this cohort—important observation.

Other Observations: Ortmeyer also studied the effect of smoking and lung function on subsequent mortality in a 10 year follow-up of a cohort of 3,726 Appalachian coal miners (136). Both smoking and ex-smoking miners were found to have increased SMR's relative to non-smokers and U.S. male controls. Miners with decreased lung function ($FEV_1/FVC \leq 70\%$) clearly had greater mortality, while those with

lung function above this level appeared to have no increase in overall mortality. This finding has recently been confirmed by Miller et al. (115).

Costello, who studied the same cohort for cardiovascular disease, reported a deficit for cardiovascular disease among working miners and only a slight excess among nonworking miners (28). Obese miners who smoked were found to be a group with a particularly unfavorable mortality. Costello's results tend to agree with previous British studies and the findings of Rockette and Higgins but are inconsistent with the findings of Enterline.

Morbidity Studies

The modern era of investigations into coal workers' pneumoconiosis began with the observation of Collis and Gilchrist on the effects of dust on coal trimmers (27). This was a combined proportional mortality and clinical study of the Coal Trimmers' Union at Cardiff, South Wales. Review of death certificates revealed marked excesses of bronchitis and pneumonia, but unlike those with silicosis, no excess mortality from tuberculosis. Reviews of several case histories revealed a radiographic pattern like that of silicosis. From these observations arose the coal workers' pneumoconiosis disease entity as separate from silicosis.

Meanwhile public concern about respiratory disease among anthracite miners in Pennsylvania lead the Governor (in 1932) to request that the U.S. Public Health Service conduct a study into the "nature and prevalence of chronic incapacitating miners' asthma" (36)(165). A thorough study of 2,711 working miners and 135 disabled miners was completed in 1934 (see Table II-22). Over 23% of the working miners had radiographic evidence of "anthracosilicosis." A clear relationship between years underground and dust concentration was established and a dust standard of 50 million particles per cubic foot (mppcf) was recommended. Pulmonary infections were also observed to be related to length of service, as was the prevalence of tuberculosis (15% in early anthracosilicosis and 43% in more advanced states). Diagnostic criteria were established and severe cardiac disease (cor pulmonale) documented among the disabled miners. A series of recommendations were made and included dust control at the source, increased mine ventilation, environmental monitoring, TB testing and control, and periodic medical examinations with

*Since this is the most recent ILO Classification, this is the only one which will be referenced for this chapter. Readers are referred to the International Labour Office, Geneva, Switzerland, for earlier Classification schemes.

Table II-20
SUMMARY OF PREVIOUS MORTALITY STUDIES OF COAL MINER COHORTS*

Study	Method	Time	Study Group	Control Group	Comment	
Kennaway and Kennaway 1936 (80)	Death certificates and census	1921-1932	Coal miners in England and Wales	General population in England and Wales	Lung cancer SMR = 59 Larynx cancer SMR = 53	
Kennaway and Kennaway 1947 (79)	Death certificates and census	1933-1938	Coal miners in England and Wales	General population in England and Wales	Lung cancer SMR = 59 Larynx cancer SMR = 66	
James 1955 (76)	Examination of the necropsies of miners with pneumoconiosis and of nonminers	1947-1952	1,827 miners with pneumoconiosis and 1,531 nonminers in South Wales	Relative risk based on the rate for all miners	Inverse relationship between the severity of pneumoconiosis and SMR for lung cancer. Very low lung cancer SMR with PMF suggests competitive risk	
Carpenter et al. 1956 (16)	Cross-sectional study	1950-1953	Residents of the Rhondda Fach, South Wales	General population of England and Wales	MINERS AND EX-MINERS Category 0 Category 1, 2, 3, A Category B, C, D Nonminers	SMR 110.2 111.0 138.6 104.1
Doll 1958 (35)	Death certificates	1948-1956	Coal miners in South	All workers in South Wales	Lung cancer SMR = 48; adjusted for other causes SMR = 58	
Cochrane et al. 1964 (22)	6-year follow-up cohort study	1951-1956	Residents of the Rhondda Fach, South Wales	General population of England and Wales	MINERS AND EX-MINERS Category 0 Category 1, 2, 3, A Category B, C, D	SMR 126.8 119.2 209.2
Goldman 1965 (46)	6-year follow-up cohort study	1951-1956	Residents of the Rhondda Fach, South Wales	General population of England and Wales	Miners and Ex-miners lung cancer SMR = 81.1, nonminers lung cancer SMR = 53.1	
Heasman et al. 1958 (55) Goldman 1965 (46)	Death certificates and information from the National Coal Board	1955	Coal miners of England and Wales	General population of England and Wales	Surface Workers Underground Workers	SMR-Lung Cancer 70.1 91.5 Other Cancer 102.0 113.4

*Source: (150) as modified

Table II-20

SUMMARY OF PREVIOUS MORTALITY STUDIES OF COAL MINER COHORTS (Continued)

Study	Method	Time	Study Group	Control Group	Comment
Stocks 1962 (158)	Death certificates and census	1949-1953	Coal miners and their wives in England and Wales	General population of England and Wales	SMR-Coal Miners Stomach Cancer 149 Bronchitis 135 Respiratory TB 119 Their Wives 154 175 145
Vinyard and Lieben 1960 (171)	Death certificates	1957-1959	Deaths with mention of pneumoconiosis in Pennsylvania		Pneumoconiosis as primary cause of death: 63% Pneumoconiosis as contributory cause of death: 37%
Lieben and Hill 1962 (92)			1959-1962		Among these: 49.1% with heart disease as primary cause 15.1% with cancer as primary cause 7.2% with pneumonia and influenza as primary cause
Enterline 1964 (38) PHS 1962	Death certificates and census	1950	Coal miners in United States	Males with working experience in U.S.	Cause of Death All Causes 195 Respiratory Disease 491 Stomach Cancer 275 Lung Cancer 192 CHD 144 TB 268 Accidents 286 SMR
Enterline 1972 (39)	Data from the Society of Actuaries	1949-1963	Policy holders in underground mining	Policy holders under standard risk	Cause of Death All Causes 172 Respiratory Disease 1,111 Cancer 80 Digestive Disease 260 Accident 626 SMR

Table II-20

SUMMARY OF PREVIOUS MORTALITY STUDIES OF COAL MINER COHORTS (Continued)

Study	Method	Time	Study Group	Control Group	Comment		
Enterline 1972 (39)	28½ year follow-up cohort study	1937-1966	533 men working in coal mines in Beckley area in 1937	United States male population	Cause of Death		
					All Causes		
					Respiratory Disease		
					TB		
					Syphilis		
					Lung Cancer		
					Digestive Cancer		
Accidents							
Liddell 1972 (94)	Death certificates and information from the National Coal Board and a sample census of mining industry in 1961	1960	Coal miners in England and Wales	Occupied and retired males in England and Wales 1959-1963	Other		
					Face Workers (SMR)	Under-ground Workers (SMR)	Surface Workers (SMR)
					Overall		
					Lung Cancer		
					Stomach Cancer		
					Bronchitis		
					Pneumonia		
					Pneumoconiosis		
					Accident (Excl. vehicle)		
					Matalo et al. 1972 (103)	Annual Gastric Cancer incidence based on Rocky Mountain States Cooperative Tumor Registry	1965-1969
Ortmeyer et al. 1973 (135)	A five year follow-up cohort study	1965/67-1970	Pennsylvania coal miners compensated for CWP	White males in Pennsylvania 1959-61	SMR	Anthracite	Bituminous
					Category 1, 2, 3, A Category B, C	108-119 143-192	82-105 120-145

Table II-20
SUMMARY OF PREVIOUS MORTALITY STUDIES OF COAL MINER COHORTS (Continued)

Study	Method	Time	Study Group	Control Group	Comment									
Creagan et al. 1974 (33)	Deaths obtained from National Center for Health Statistics. Population estimated from census	1950-1969	Residents in 23 coal mining counties in U.S.	Residents in non-coal mining counties in the same states and matched by educational level	Increase in risk ratio among coal county residents for lung and stomach cancer risk ratios, but decreased risk ratios for leukemia, colon, cervix, and breast.									
Costello et al. 1974 (29)	10-year follow-up cohort study	1962/63-1971	3,726 Appalachian coal miners (the 1950 PHS CWP study)	Male population in United States 1968	Lung cancer SMR = 67; 22 of 24 lung cancer deaths had smoking history.									
Ortmeyer et al. 1974 (136)	10-year follow-up cohort study	1962/63-1971	3,726 Appalachian coal miners (the 1950 PHS CWP study)	Male population in United States 1968	SMR for all causes = 104. Increased in association with smoking (current or ex-smoker), ex-mining status, and lung function (FEV ₁ /FVC < 70%).									
Costello et al. 1975 (28)	10-year follow-up cohort study	1962/63-1971	3,726 Appalachian coal miners (the 1950 PHS CWP study)	Male population in United States 1968	<table border="1"> <thead> <tr> <th><i>Cause of Death</i></th> <th><i>Working Miners (SMR)</i></th> <th><i>Ex-Miners (SMR)</i></th> </tr> </thead> <tbody> <tr> <td>All Heart Disease</td> <td>73</td> <td>104</td> </tr> <tr> <td>Ischemic Heart Disease</td> <td>73</td> <td>105</td> </tr> </tbody> </table>	<i>Cause of Death</i>	<i>Working Miners (SMR)</i>	<i>Ex-Miners (SMR)</i>	All Heart Disease	73	104	Ischemic Heart Disease	73	105
<i>Cause of Death</i>	<i>Working Miners (SMR)</i>	<i>Ex-Miners (SMR)</i>												
All Heart Disease	73	104												
Ischemic Heart Disease	73	105												
Jacobsen 1976 (75)	Prospective cohort mortality study	1958-1972	<p>Sample of National Coal Board cohort for whom vital status was known:</p> <p>a) 100% sample of those with CWP by radiograph (3,523)</p> <p>b) 50% sample of those remaining (13,786)</p> <p>Total cohort = 17,309</p>	Registrar General mortality for all males—England, Scotland, and Wales. Internal sub-group comparisons.	Cancer of digestive organs, respiratory disease and bronchitis mortality appear to be dose related. Simple CWP not associated with increase in mortality except among younger miners. Respiratory symptoms and smoking associated with increased mortality. No evidence of an association between lung cancer and coal mine dust exposure. (See discussion).									

Table II-20
SUMMARY OF PREVIOUS MORTALITY STUDIES OF COAL MINER COHORTS (Continued)

Study	Method	Time	Study Group	Control Group	Comment
Rockette (150)	Retrospective cohort mortality	1959-1971	10% sample of 550,000 UMWA Welfare and Retirement Fund records yielding 23,233 eligible for benefits from the fund on January 1, 1959. Vital status determined as of December 31, 1971.	Total U.S. male population	Excess mortality from accidents; several categories of respiratory disease, and stomach cancer. (See Table III-21).
Miller, Jacobsen, and Steele (115) 1981	Prospective cohort study	1958-1980	Further follow-up of the Jacobsen cohort above 22 to 26 years from identification	As above	Miners with Category A PMF at the start of follow-up showed a considerably higher mortality than men without PMF. Survival rates for Category 1 simple CWP (all ages over 24) were reduced compared to men with Category 0 radiographs. There was no trend to increasing mortality with increasing category of simple CWP. Mortality from pneumoconiosis, bronchitis, and emphysema was more severe among those with heavy dust exposure before study start-up. Digestive system cancer was related to increasing dust exposure and increasing pneumoconiosis. No evidence of increased risk of lung cancer. Smoking miners had 5½ times the lung cancer mortality of nonminers (subgroup data). Those with low levels of FEV ₁ had increased mortality attributable to lung cancer, bronchitis and emphysema (55 to 64 at start-up), pneumoconiosis, other respiratory disease, and ischemic heart disease.

Table II-21
OBSERVED AND EXPECTED DEATHS, AND STANDARDIZED
MORTALITY RATIOS FOR COAL MINERS FOR SELECTED
CAUSES OF DEATH (N = 22,998)

Cause of Death	Observed	Expected	SMR*
All Causes	7,628	7,506.1	101.6
All Malignant Neoplasms	1,223	1,252.2	97.7
Benign and Unspecified Neoplasms	14	14.4	97.5
Major Cardiovascular Diseases	4,285	4,501.2	95.2*
Bronchitis	27	31.5	84.8
Acute Bronchitis and Bronchiolitis	1	2.5	—
Chronic and Unqualified Bronchitis	26	29.0	89.7
Influenza	28	14.8	189.6*
Pneumonia	217	232.3	93.4
Emphysema	170	118.3	143.7*
Asthma	32	18.3	174.9*
Tuberculosis	63	43.3	145.5*
Syphilis	16	13.1	122.3
Other Infective and Parasitic Disease	13	17.6	74.1
Diabetes Mellitus	64	110.2	58.1*
Peptic Ulcer	42	58.7	71.6*
Cirrhosis of Liver	64	104.9	61.0*
Cholelithiasis, Cholecystitis, and Cholangitis	22	16.7	132.0
Nephritis and Nephrosis	42	46.2	91.0
Accidents	408	283.0	144.2*
Suicides	81	81.3	99.6
Homicides	30	26.1	115.1
Ill-Defined Causes	162	86.2	187.9*
All Other Causes	625	459.5	136.0*

*Standardized Mortality Ratio (SMR) is significantly different from 100 at the 5% level.

Source: (150)

an annual x-ray. Unfortunately, many of these recommendations were not adequately implemented and unlike Britain, where early studies led to industry-wide compensation programs and further epidemiologic investigation, neither broad legislation nor immediate further investigation followed. Indeed, studies by Clarke and Moffett in Southern Appalachia and the U.S. Public Health Service in Utah in the early 1940's, suggested that pneumoconiosis was relatively uncommon among bituminous miners (see Table II-22) (19)(42).

No other important epidemiological studies were published until 1963 when Hyatt studied a random sample of miners and ex-miners in Raleigh County, West Virginia (65). This study established, for bituminous miners of that region, the importance of coal mine dust exposure as a cause of both pneumoconiosis and lung impairment.

Simple CWP was found in 46% and PMF in 7% of those surveyed and CWP was also found to be strongly related to years underground. Pulmonary impairment was observed among those with Category 3 simple CWP and PMF. Respiratory symptoms were found to be related to lung function which was itself related to years underground and unexplained by differences in age, smoking, or category of pneumoconiosis.

Thus, the severity of CWP and major risk factors among U.S. anthracite and bituminous miners were documented by 1963. The prevalence of the disease throughout the U.S. coal fields, quantitation of risk factors, and further evaluation of dose-response relationships awaited documentation by a flurry of epidemiological studies in Britain, Germany, and the United States.

Prevalence of CWP: A series of studies by the Pennsylvania Board of Health (93)(104)(105)

Table II-22
MORBIDITY STUDIES OF COAL MINERS IN THE UNITED STATES

Study	Date	Population Studied	Prevalence of CWP	Comment
Office of Industrial Hygiene and Sanitation U.S. Public Health Service Dreesen, et al. (36)	1934	Pennsylvania anthracite miners, 2,711 working in 3 representative mines; 135 disabled ex-miners	23.7% "anthrasilicosis" 100.0% "anthrasilicosis"	Documented the seriousness of CWP in United States. Established different dose-response relationships for coal and rock workers. Infection and cor pulmonale important complicating factors.
Clarke and Moffett (19)	1941	744 Southern coal miners of a single mine. Exposure 1 + years	3.1% "presilicotic" 1% "silicotic nodulation"	TB a common complication (7.4%). Clear increase in "nodulation" with years underground.
U.S. Public Health Service Flinn et al. (42)	1942	507 Utah bituminous coal miners	3.2% "anthracosilicosis"	13 of 16 cases with many years underground. No case with less than 10 years experience. Two cases with under 20 mppcf.
Hyatt, et al. (65)	1963	Stratified random sample of miners and ex-miners from Raleigh Co., W. Va. n = 267 ages 45-58	46% Simple and PMF 7% PMF	58% with respiratory symptoms associated with years underground but not CWP. Increased lung impairment with Category 3 and PMF. Decreasing lung function with years underground independent of smoking and aging.
Lieben et al. (93)	1961	4,182 Central Pennsylvania coal miners—medium and higher rank coal	30% overall 40% with CWP had PMF	Included working miners with 20 or more years of mining and retired miners. 25% participation.
McBride et al. (104)	1963	8,237 Western Pennsylvania bituminous coal miners—low rank coal	11% overall 37% with CWP had PMF	Included miners with 20 years or more mining and retired miners. 68% participation.

Table II-22
MORBIDITY STUDIES OF COAL MINERS IN THE UNITED STATES (Continued)

Study	Date	Population Studied	Prevalence of CWP	Comment															
McBride et al. (105)	1966	1,858 anthracite miners participating in Pennsylvania Division of Occupational Health Surveys	30% overall 10% < 30 years work 50% > 40 years work 80% > 40 years work and retired	A third of the men without CWP reported severe dyspnea. Cough related to years exposure and age. 70% of men over 55 had FEV ₁ < 70%.															
U.S. Public Health Service Lainhart et al. (87)	1962-65	Sample of 97 bituminous Appalachian coal counties, large and small mines: working miners = 617 nonworking miners unemployed = 617 pensioned = 574. Pulmonary function on: working miners = 2,342 nonworking miners = 1,028	<table style="margin-left: auto; margin-right: auto;"> <tr> <td></td> <td style="text-align: center;">Non-Working Miners</td> <td style="text-align: center;">Working Miners</td> </tr> <tr> <td>No CWP</td> <td style="text-align: center;">84.9</td> <td style="text-align: center;">74.9</td> </tr> <tr> <td>Suspect</td> <td style="text-align: center;">5.3</td> <td style="text-align: center;">6.9</td> </tr> <tr> <td>Simple</td> <td style="text-align: center;">6.8</td> <td style="text-align: center;">9.2</td> </tr> <tr> <td>PMF</td> <td style="text-align: center;">3.0</td> <td style="text-align: center;">9.0</td> </tr> </table>		Non-Working Miners	Working Miners	No CWP	84.9	74.9	Suspect	5.3	6.9	Simple	6.8	9.2	PMF	3.0	9.0	Association between dyspnea and productive cough and years underground and smoking. Years underground appeared to influence lung function more than smoking. Moderate effect of bronchitis and CWP on lung function. Marked association between dyspnea and lung function.
	Non-Working Miners	Working Miners																	
No CWP	84.9	74.9																	
Suspect	5.3	6.9																	
Simple	6.8	9.2																	
PMF	3.0	9.0																	
U.S. Public Health Service Enterline (40)	1963-65	Community study of Mullens and Richwood, W. Va., with a matched sample of miners and ex-miners and nonminers and their wives from each community	Mullens = 13.85% Richwood = 6.3%	Excessive respiratory symptoms among miners and wives relative to nonminers and nonminer wives. Reduced lung function among miners only in Mullens not Richwood. No difference in lung function of wives.															
Higgins, et al. (61)	1968	Cross-sectional study of three mining communities in Marion Co., W. Va. n = 957	Simple CWP = 29/448 PMF = 4/448	Except among older miners, respiratory symptoms and FEV ₁ did not differ between miners and nonminers. Lung function in this West Virginia sample appeared to be better than two British communities studied earlier.															

Table II-22
MORBIDITY STUDIES OF COAL MINERS IN THE UNITED STATES (Continued)

Study	Date	Population Studied	Prevalence of CWP		Comment			
U.S. Public Health Service First Round National Study of Coal Workers' Pneumoconiosis (131)	1969-71	29 bituminous and 2 anthracite mines selection based on seam, mining method, number of miners, and retrospective dust data. n = 9,076	Total Anthracite Appalachia Midwest West	Total PMF 60.0 14.3 30.0 2.1 25.0 2.9 10.5 0	Respiratory symptoms and lung function associated with region, years underground, and smoking.			
				Category 0 92.0 1 4.9 2 1.9 3 0.2 PMF 1.0				
				U.S. Public Health Service Second Round National Study of Coal Workers' Pneumoconiosis (132)		1972-75	Same mines as in round 1. Some mines closed and Some new mines selected n = 9,343	Previous findings confirmed. Flow rates, especially of larger lung volumes, associated with years underground and bronchitis and smoking. Time between rounds precludes meaningful assessment of progression.
				Higgins, et al. (59)		1963-72	Follow-up community of Mullens and Richwood. Miners and ex-miners and nonminers.	Mullens Richwood Miners 18.1(4.5) 9.9(1.5) Ex-Miners & Non-Miners 3.8(0.3) 0.3(0.0)

documented an increasing gradient in CWP prevalence from western to eastern Pennsylvania—from 11% in the West to 35% in Central and Eastern Pennsylvania mines. The U.S. Public Health Service studied 97 Appalachian coal counties and found nearly 10% of working miners and 18% (9% with PMF) of nonworking miners to have CWP (87).

The NIOSH National Study of Coal Workers' Pneumoconiosis was the first U.S. industry-wide study of this disease (131). It was designed as a prospective study of some 30 mines and over 9,000 miners and included PA and lateral chest radiographs, spirometry, and a standard MRC questionnaire. CWP prevalence in the first round of this study, which ran from 1969 to 1971, anteceded outward migration of a substantial proportion of miners with many years underground and relatively high dust exposures. Still, the prevalence of CWP reported was a good deal higher than previously reported (see Table II-22). This may in part be attributable to the use of new international standards (UICC 1968) for the interpretation of radiographs for the pneumoconioses and reader variation. In the second round of this prospective study, the study population was quite different due to the outward migration of older miners and an influx of young miners (7)(113). International radiographic standards for the interpretation of the pneumoconioses were again changed (1971 ILO/UC Classification), as were the radiograph readers. The change in radiographic standards is thought not to have contributed to lower prevalence rates (132). Evidence is presented elsewhere from the National Coal Miner Health Surveillance Program, that the prevalence of CWP by years underground did not differ between round one and round two; thus, reduction in dust level during this brief interval did not appear to influence CWP prevalence (113). Recent surveillance results are presented in Table II-24 and suggest a slight decrease in CWP prevalence—below 5% among working miners. Whether this is in part due to dust controls implemented in the early 1970's, or principally attributable to shifts in the mining work force, is not yet clear.

Dose-response studies: Dreesen and colleagues in their 1934 study of anthracite miners not only documented a marked association between prevalence of "anthracosilicosis" and years underground, but also documented a clear

dust and pneumoconiosis relationship (165). Men exposed to between 5 and 99 million dust particles per cubic foot of air over 25 or more years underground were found to have an approximate 7% prevalence of pneumoconiosis. This prevalence increased in each dust category to reach nearly a 90% prevalence over 25 years among men exposed to 300+ million dust particles per cubic foot of air.

Numerous later cross-sectional studies confirmed this observation using years underground as a surrogate for dose (see Table II-22). It was, however, not until the first 10 years of observations were completed by the Pneumoconiosis Field Research (PFR) Unit in Great Britain, that dose-response based on gravimetric sampling of respirable dust was established (73). That study was based on findings among 4,122 coalface workers at 20 collieries of the original 25 selected in 1953. Results of that study suggested a negligible risk of developing Category 2/1 CWP over a working lifetime below 2.0 mg/M³ (See Figure II-23). These results were provided to the U.S. Congress and were instrumental in the mandating of the 2 mg/M³ standard by the 1969 Act (see Table II-13). Jacobsen et al., also reported that smoking did not significantly affect the attack rate of pneumoconiosis or significantly alter the dose-response relationship (71).

The 20 year follow-up of miners in 10 of the PFR original collieries was recently reported (64). The original dose-response relationship was confirmed unambiguously, but the long-term risks were slightly greater (one to two percentage probability units) than estimated in 1969 (see Figure II-23). Large variations were noted between collieries and were not accounted for by quartz content, coal rank, or any other risk factors measured. Further, there was no pattern to suggest that quartz affected the probability of developing simple CWP. Jacobsen (1980) has recently, however, reported an association between PMF and quartz content based upon a case-control study arising from prospective data (72). In 1982, results from the third round of the NIOSH National Worker Health Surveillance Program and National Study of CWP, together with extensive dust data available from MSHA and NIOSH, should provide a U.S. assessment of approximately 10 years of exposure (following the 1969 Act).

Table II-23
RESPIRABLE DUST LEVELS (Mg/M³)
HIGH RISK AND SELECTED OCCUPATIONS

	1968	1973	1976	1977
Jacksletter		4.2	1.9	1.9
Longwall		2.6	1.8	2.2
Continuous Miner Operator	6.5	2.1	1.3	1.3
Roofbolter	3.9	2.1	1.4	1.2
Cutter Operator	5.9	1.8	1.2	1.1
Loader Operator	6.0	2.7	1.2	1.3

Source: (113)

PROBABILITY (%)
OF DEVELOPING CATEGORY
2/1 OR MORE

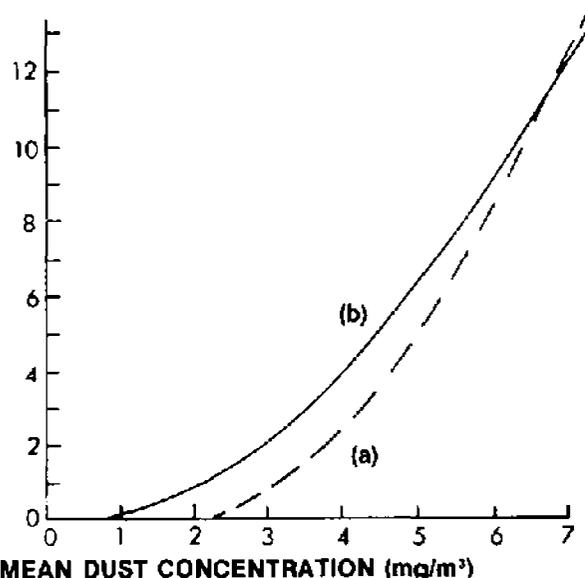


Fig. II-23. Lines (a) and (b) are estimates of probabilities of developing Category 2 or 3 of simple pneumoconiosis over an approximately 35-year working life at the coalface, in relation to the mean dust concentration experienced during that period. (a) is based on 10 years of data, Interim Standards Study, Pneumoconiosis Field Research. (b) is update of (a), based on 20 years of data, Pneumoconiosis Field Research.

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Bronchitis: Historically, bronchitis and associated respiratory infections have been prominent respiratory findings among miners exposed at high dust levels. This has, however, not been

a uniform finding in retrospective cohort mortality studies and has not been confirmed (nor looked at closely) in pathological studies. Respiratory infections and bronchitis were prominent findings in the 1934 U.S. Public Health Service study of anthracite miners (165). The symptoms of chronic cough, phlegm, and dyspnea have been consistently increased among underground miners and have usually been associated with years underground and smoking in more recent cross-sectional studies (40)(65)(87)(131)(132). Hyatt observed that many miners appeared to acquire their symptoms within the first year of employment and retain them for years following (65). Ashford et al. (1970) made similar observations on approximately 30,000 miners studied by the Pneumoconiosis Field Research Unit of the National Coal Board (6). They suggested that respiratory symptoms (persistent cough, persistent phlegm, breathlessness, and wheeze) were associated with radiographic evidence of pneumoconiosis, smoking, and age (neither years underground nor dust levels were controlled). They further suggested that those with bronchitis (persistent cough and phlegm) differed from those with breathlessness and wheeze. Rae et al. assessed chronic bronchitis and dust exposure among the 4,122 coal-face workers previously studied by Jacobsen, thus providing the first good estimate of dust exposure for such an assessment (142). A statistically significant association was found between increasing respirable dust concentration and increasing bronchitis among men in the 25-34 and 35-44 year age groups. Smoking and the presence of pneumoconiosis was associated with increased bronchitis prevalence in all age groups. The association between smoking and phlegm production, and the

Table II-24
COAL WORKERS' PNEUMOCONIOSIS IN ROUND THREE OF
THE NIOSH NATIONAL COAL WORKERS' HEALTH SURVEILLANCE PROGRAM*

Years Mining	CAT 0	CAT 1	CAT 2	CAT 3	CAT PMF	Total
0-9	39,050 98.90%	416 1.05%	14 0.04%	1 0.00%	2 0.00%	39,483
10-19	6,167 93.185%	424 6.40%	22 0.332%	1 0.015%	4 0.060%	6,618
20-29	2,228 82.396%	410 15.163%	52 1.923%	5 0.185%	9 0.333%	2,704
30-39	2,094 71.737%	628 21.514%	130 4.454%	9 0.308%	58 1.987%	2,919
40 +	369 66.606%	135 24.368%	32 5.776%	4 0.722%	14 2.527%	554
Total	49,908 95.467%	2013 3.851%	250 0.478%	20 0.038%	87 0.166%	52,278

*10/1/78 through 12/15/80

attack rate of CWP has also been studied by Jacobsen and colleagues (71).

Higgins conducted four mining community studies of respiratory disease in Britain (62) and the United States (60)(61). Excesses in bronchitis and breathlessness among miners and ex-miners were common findings, although the excesses were small in the U.S. study (Marion Co., W. Va.). Kibelstis and colleagues, based on questionnaire data from the first round of the NIOSH National Study of Coal Workers' Pneumoconiosis, reported a clear trend in bronchitis prevalence (83). Hankinson et al., in an analysis of second round data from the National Study of Coal Workers' Pneumoconiosis, demonstrated a bronchitis effect on lung function, particularly flow rates at higher lung volumes, in addition to an independent smoking effect (51). Rogan et al. reported similar effects. Rogan suggested that symptoms, once contracted, caused further reductions in lung function, even after dust exposure ceased (152). Finally, in a follow-up study of an earlier U.S. Public Health Service study in Mullens and Richwood, West Virginia, Higgins reported increased respiratory symptoms among miners and ex-miners as compared to nonminers (59). He

concluded that independent and additive smoking and mining effects were operative.

Exposure to diesel emissions, a potentially important hazard, is now being observed with greater frequency in U.S. underground coal mines. Although American mines have traditionally been electrically powered, foreign mines have utilized diesel haulage equipment for decades. Possible diesel related health effects among coal miners have only recently been studied. Reger et al. studied over 800 underground U.S. coal miners whom he matched to other miners with similar smoking and dust exposures but who had worked only in electrically powered mines (147). Diesel exposed miners were found to have more bronchitis, which increased with years underground, and lower lung function than the reference group. However, surface miners at diesel mines also showed similar, but smaller trends, making interpretation difficult. The authors suggested that caution should be used in introducing diesels pending prospective epidemiological evaluation and other studies.

Lung Function: Seriously impaired lung function was recognized among miners with advanced CWP and especially PMF at the time

of the initial Public Health Service studies in 1934 (165). It was, however, not until the 1950's that pulmonary function testing in epidemiological surveys of working populations began contributing important quantifiable data on lung function. Hyatt and colleagues were the first to apply sophisticated lung function measurements in an epidemiological study of American coal miners (65). A volume displacement body plethysmograph was used and FEV₁, FVC, MMEF and RV/TLC ratio were reported. A marked association was found between all symptoms measured (phlegm, cough, wheeze, aggravation of symptoms by weather, episodes of cough and phlegm, and dyspnea) and all four measures of lung function. Increasing numbers of symptoms were similarly associated with a progressive decline in all four measures of lung function. Years worked underground was found to exert a significant and independent deleterious effect on lung function. Smoking was found to also be an important risk factor which appeared to work in an additive fashion to increase respiratory symptoms and decrease lung function.

These general observations have since been confirmed by larger, more representative cross-sectional and prospective studies of coal miners and studies of coal mining communities. Studies of lung function included in the Public Health Service study of 97 coal-producing Appalachian counties confirmed the findings of Hyatt in regard to the influence of years underground on FEV₁ and FVC and the additive effect of smoking (87). It was concluded that smoking did not exert the major effect in this study. A review by Higgins (1971) of chronic respiratory disease in four mining communities—while controlling for other important lung function risk factors—concluded that excesses in respiratory symptoms and decreased lung function (FEV₁) were commonly found among miners and ex-miners compared with nonminers living in those communities (60).

Ventilatory capacity and lung volumes were studied in the first round of the National Study of Coal Workers' Pneumoconiosis by Morgan et al. (122). No relationship between ventilatory capacity and radiographic category of simple CWP was found; however, PMF was associated with definite impairment. In addition, significant geographic variation (lung function tending to be worse among anthracite miners and best among western miners) was observed.

In an effort to better characterize the nature of lung function changes and the contribution of bronchitis among working coal miners, Hankinson et al. drew four well-matched groups of 428 miners from a total of over 9,000 working miners studied in the second round of the NIOSH National Study of Coal Workers' Pneumoconiosis (51). This provided a bronchitis and smoking specific analysis in which age and height were matched and allowed comparison and quantification of FEV₁, FVC, peak flow, four measures of flow rates (\dot{V}_{max} 25, 50, 75, 90), RV, and TLC. While both bronchitis alone and smoking alone produced significant adverse changes in most measures of lung function, smokers with bronchitis consistently showed the most impairment among these four groups. Smokers had greater decreases in flow rates at higher lung volumes and greater increases in RV and TLC, suggesting a prominent small airway or alveolar process, while measures more indicative of large airway function (FEV₁ and \dot{V}_{max}_{25} and 50) were relatively more marked among those with bronchitis.

Quantitation of dust and smoking effects on declines in lung function over time have been attempted, based on the British Pneumoconiosis Field Research (PFR) data. An initial report by Rogan and colleagues was based on a sample of face workers who had been followed for at least 10 years by the PFR (152). Based on these results it was calculated that the effect of smoking 15 cigarettes/day over 40 years appeared comparable to experiencing a dust concentration of 14 mg/M³ over that same period. The authors cautioned that this estimate may have underestimated the dust effect because of the highly selected nature of the sample. One criticism of the statistical analysis of that paper was the method used to standardize for smoking, even though there was no evidence of a significant interaction on lung function between smoking and dust exposure (21). Reanalysis of this data by smoking groups confirmed that pooling smoking and nonsmoking miners tended to underestimate the smoking effect with increasing age (75). Cochrane further suggested that a follow-up study of ex-miners in various regions would provide a better estimate of risk factor effects (21). Such a follow-up study was completed by the Institute of Occupational Medicine and reported in 1979. This sample was based on 12 of the original 24 mines studied, and of 3,870 miners examined, 2,094 were ex-miners

at the time of follow-up (112). Analysis of this data found that the effect of dust exposure on FEV₁ was at least half as much again and perhaps as much as twice as marked as the original Rogan estimate. Thus, the concern expressed by Rogan in regard to the selected nature of the face-worker sample was well justified.

The relative importance of coal mine dust exposure and smoking on decline in lung function among coal miners has been an important but controversial issue. It was reported, and is often quoted, that the effect of smoking is five times that of coal dust (83). Morgan asserts in a recent review (117) that "smoking has about five to ten times greater effect on ventilatory capacity," and more recently that "cigarette smoking is between six and ten times more important," citing the aforementioned review (83) (118). Yet examination of the original Kibelstis et al. data does not provide unqualified support for that conclusion. An assumption was apparently made that surface miners have negligible coal mine dust exposure. Such an assumption is faulty on two counts; one, because many surface miners have had significant previous underground exposure, and two, because certain surface jobs themselves result in significant dust exposure. Thus, there is not an adequate unexposed control.

However, if one takes the same data from the first round of the National Study of Coal Workers' Pneumoconiosis and compares it to the NIOSH external blue collar control population* (using the same methods as used in the NSCWP), and applies the spirometric standards for significant impairment used by the Department of Labor (FEV₁ \leq 60% predicted), one finds an estimated relative risk for smoking of 2.0 and for dust exposure, 2.1; i.e., their effects on this indicator of impairment appear to be similar. It is important to note that the first round of the NSCWP was conducted prior to general availability of federal benefits which provided the means for many impaired miners to leave mining.

Higgins et al. provide prospective data, which is externally controlled, in their study of Mullins and Richwood (59). In this study, separate mining and smoking effects were documented. The annual decline in FEV₁ was slightly greater for smoking (smoking nonmining men compared to nonsmoking nonmining men) than the annual decline in FEV₁ for all miners com-

pared to all nonminers.

These observations are consistent with the prospective British studies. As previously reviewed, reanalysis of the Rogan et al. data (152) suggested that the smoking effect had been underestimated (75). However, analysis of a less selected cohort, which included ex-miners, found that the effect of coal mine dust exposure was one and one half to two times as great, but that the reduction in FEV₁ attributable to smoking was no more marked than found previously by Jacobsen (70)(112). From review of these studies it appears that the smoking to dust effect ratio decline in FEV₁ is between one and two. It must be stressed that these are average values based on population studies. Older miners who have many years underground may have significantly more dust exposure than the average and therefore may be expected to be more affected by dust than smoking. Alternatively, younger miners will likely experience much less dust exposure; hence without similar reductions in smoking exposure, smoking would be expected to become a much more powerful risk factor. It should further be noted that one should not be surprised that a very high proportion of impaired coal miners have a history of cigarette smoking (112). This follows from two well established findings: 1) that over 80% of U.S. coal miners have a smoking history, and 2) that smoking significantly adds to the effect of dust exposure on decline in lung function.

In summary, coal mine dust exposure has been found to have an unambiguous, adverse effect on lung function, which is separate and additive to that of the other major (controllable) risk factor, smoking. Quantitation of the relative contributions of cigarette smoking and coal mine dust exposure have been difficult because good dust data is usually not available and because study populations are invariably selected (and thus effects underestimated) to some extent. It is safe, however, to conclude that both coal mine dust and cigarette smoking are important risk factors which operate additively to decrease lung function in a dose-response fashion.

Epidemiology of Graphite and Carbon

Black Exposure: While both graphite pneumoconiosis and carbon pneumoconiosis are well documented clinically, there is only limited epidemiological data. It is known that graphite miners may develop pneumoconiosis, both simple and PMF, after 15 years exposure. Most of these reports have come from Sri Lanka (Ceylon)

*Technical Report to Director, NIOSH: Epidemiologic Study of Normal Blue Collar Workers, September 1981.

which is a major exporter of natural graphite (34)(144). Ronashinha and Uragoda studied a large graphite mine employing 344 underground and surface workers (144). Pneumoconiosis, which was described as being composed of both rounded and irregular opacities in mid and upper lung zones, was reported in 22.7% of those surveyed. Digital clubbing was found in 21.9% and specific attention was drawn to the absence of bronchitis and tuberculosis. Tuberculosis was reported among three miners in another mine but was not considered to be an increased hazard in graphite mining because of the relatively low silica content (163).

Among the reported respiratory effects of carbon black exposure are pneumoconiosis, bronchitis, and emphysema (130). Most of the epidemiological studies have involved limited numbers of workers. Dust exposures have been relatively high, or not reported, making interpretation difficult (130). Retrospective cohort mortality studies have raised the possibility that carbon black may itself be a carcinogen or bind other carcinogens (66-68). Apart from the clear evidence that carbon pneumoconiosis may occur among those exposed to carbon black, there is little morbidity data available. Valic reported a radiographic study of 35 Yugoslavian workers exposed to carbon black an average of 12.9 years (respirable dust concentrations = $7.2 \pm 1.8 \text{ mg/M}^3$) (169). A risk-factor-matched, non-exposed control group was also studied. Initial lung function testing (FEV₁ and FVC) on both groups in 1964 revealed no significant differences. However, when tested again in 1971, a significant decline in lung function was noted in those exposed compared to controls. Although the authors raised questions about the adequacy of the control group (they lived near the carbon black plant), the declines in lung function among carbon black workers were still significantly greater than the decline expected in normal populations over time. Valic also reported that 17.1% of the 35 workers showed evidence of a fine nodular pneumoconiosis in the mid and lower lung zones.

PATHOLOGY AND PATHOGENESIS OF COAL WORKERS' PNEUMOCONIOSIS

The primary lesion of coal workers' pneumoconiosis (CWP) is the coal macule. This lesion was first clearly described by Gough (47) and by Heppleston (58). Before this time, opinions on specific lung pathology in coal workers were

confused. Recognition and clear description of the pathology depended on the development of methods for examining sections of whole lung fixed in inflation (49). Using this technique, this earlier work has been confirmed in all the major coal producing nations. In whole lung sections, the coal macules appear as black areas 1-4 mm in diameter (Figure II-24). The smaller ones are usually circular while the larger ones are more irregular and often stellate. The lesions are usually symmetrically distributed in both lungs with a greater concentration in the upper lobes. Adjacent to the macule the airspaces are enlarged, constituting focal emphysema. These two features were considered pathognomic for coal workers' pneumoconiosis by the Pneumoconiosis Committee of the College of American Pathologists (85). Focal emphysema usually only involves a region of 1-2 mm around the pigmented macule. Both the macule and the associated focal emphysema occur in the region of the first order respiratory bronchioles. Microscopically, the pigment is found within macrophages both inside the airspaces and in the connective tissue around the respiratory bronchioles (Figure II-25). In longitudinal sections the pigment-laden cells thinly sheathe the walls of the bronchiole and may be relatively inconspicuous. In transverse section, the lesions are much more obvious. The macrophages are often densely packed and completely fill the airspaces. A fine reticulin fibrosis is present in the lesion. Collagen is either absent or sparse. There is loss of elastic fibers in the airways involved in the emphysema. In coal workers who have lived in retirement for many years, the alveoli within a macular lesion may no longer be totally filled with pigment-laden macrophages suggesting some degree of clearance (Figure II-26). The macules are nonetheless recognizable by the pigment in the interstitial tissue and the surrounding focal emphysema. A minor vascular change associated with the coal macule has been reported (128). This consists of an increase in arterial medial muscle due to hypertrophy of the muscle fibers as the artery transverses the lesion. The authors did not consider these vascular changes to have much functional significance. The mechanism whereby the coal macule develops is considered to be an overwhelming of normal lung particle clearance mechanisms by the heavy dust burden experienced. The reticulin fibrosis and possibly the emphysema may be due to the damaging effects of released macrophage



Figure II-24. 57-year-old coal miner who worked 31 years underground as a trackman, smoked 20 cigarettes per day. Whole lung section shows mild simple coal workers' pneumoconiosis. The macules, which are more numerous in the upper zone, are outlined by mild focal emphysema.



Figure II-25. High power micrograph of alveolar macrophage within alveolus from the lungs of an active miner. The majority of the phagocytosed particles are coal mine dust. Hematoxylin and eosin x 585.

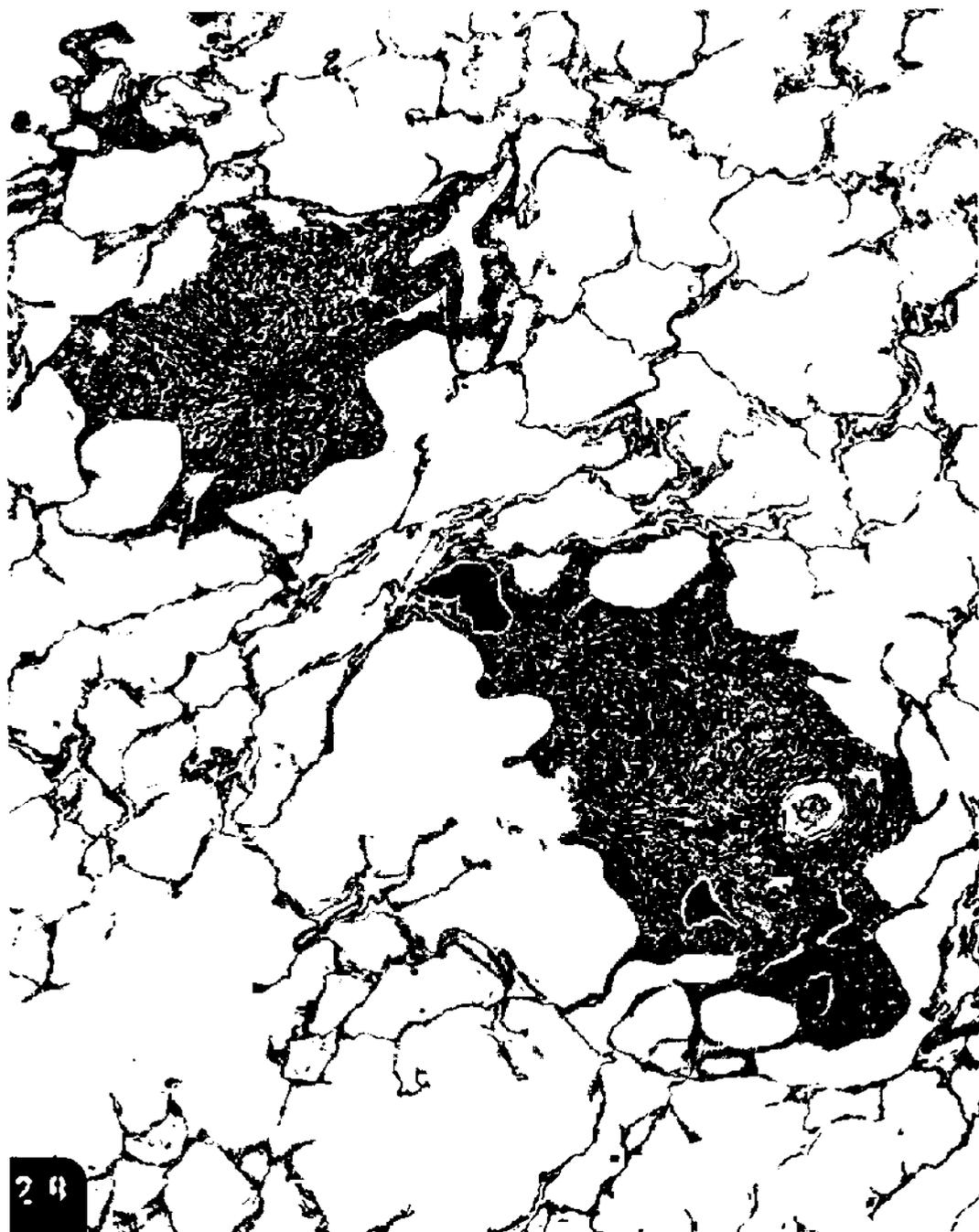


Figure II-26. Coal macules in the walls of respiratory bronchioles. The macules are composed of macrophages, coal mine dust and reticulin. There is minimal air space enlargement (focal emphysema) around the macule. Hematoxylin and eosin \times 100.

lysosomal enzymes.

Even in nonoccupationally dust exposed individuals, pigmented lesions are found in the lung. This is presumed to be derived from atmospheric pollution and is more marked in urban as compared with rural dwellers. These "normal" pigment lesions vary in size up to about 4 mm. The pigment is contained within macrophages both on the walls of alveolae and in the stroma of the bronchiolar wall. In differentiating these lesions from the typical macule of coal workers' pneumoconiosis, three factors are useful. The "normal" pigment lesion is not usually associated with focal emphysema and the alveolae are not completely filled with pigment-laden macrophages. In addition, the pigment particles in the nonoccupationally exposed individuals are black and rounded while coal dust particles are angular, often translucent, and of a lighter yellow or brown color.

The coal macule is soft and is not palpable on examination of unfixed lung. This differentiates coal macules from the nodular lesions of CWP. A number of different nodular lesions are recognized in the lungs of coal workers. These are micro and macronodular lesions of simple coal workers' pneumoconiosis, progressive massive fibrosis, Caplan's lesion, and because miners are also exposed to crystalline silica from the strata surrounding the coal seam, the nodules of simple and conglomerate silicosis. In addition, the nodular lesions of the infective granulomata (tuberculosis and histoplasmosis, in particular) occur in coal miners, as in any other population, and require differentiation by classical histologic and microbiologic methods.

The nodular lesions of simple CWP are palpable because of their collagen content and sometimes because of calcification. They are divided for descriptive purposes into micro-nodular (up to 7 mm in diameter) and macro-nodular (greater than 7 mm in diameter) (85). The nodules are dark gray or black and are usually centriacinar in location (Figures 11-27A and 11-27B). Less frequently nodules are in the subpleural or peribronchial regions. They are often rounded but may have irregular prolongations into the surrounding tissue. They are commonly, but not invariably, associated with scar emphysema which in some individuals can be extensive. On microscopy the major difference between the nodular and macular lesions is the larger size and presence

of hyalinized collagen in the former (Figure 11-28). The collagen bundles are usually arranged in an interlacing or haphazard pattern and this feature is useful for distinguishing the nodules from silicosis where the collagen is concentrically arranged. The nodular lesions are believed to develop from macules but it is clearly impossible to demonstrate such progression in an individual coal worker. The reasons why nodules contain more collagen are not known, but the possibility that silicates—or the more toxic silica—are involved must be considered.

Some occupations within the mine are more commonly exposed to silica. These are the roof-bolters who are exposed to dust derived from the overburden, the motormen who, in some mines, used sand to provide traction for their vehicles, and drillers in surface coal operations (the latter may have acute silicosis). Such coal workers may have the classical lesions of silicosis. These nodules have smoother borders than the typical nodular lesions of CWP and, though they may contain black pigment, are often paler and may have a relatively pigment-free center (Figure 11-29). They are more difficult to cut than CWP lesions. The arrangement of collagen is orderly and has a laminated or whorled pattern. Coalescence of adjacent silicotic nodules may occur resulting in conglomerate silicosis. Calcification in the hilar lymph nodes is common in silicosis. It may be of the egg shell type as described on radiologic examinations or may be randomly distributed.

Complicated coal workers' pneumoconiosis or progressive massive fibrosis (PMF) is diagnosed radiologically when an opacity 1 cm or greater is found. This conforms to the anatomic definition set out in the regulations of the National Coal Workers' Autopsy Study (166). However, the Pneumoconiosis Committee of the American College of Pathologists recommended a 2 cm standard as being more appropriate for pathological studies (85); a 3 cm standard is used in England (77). PMF occurs on a background of simple CWP, more commonly of the nodular rather than the macular type. The extent of simple CWP is usually considerable, but can consist of relatively few nodules and macules in some individuals. The lesions of PMF are most commonly situated in either upper lobe or the apical segments of the lower lobes. The lesions are usually asymmetrical in the two lungs.



Figure II-27A. Coal miner, no detailed history available. (A) Whole lung section shows macules, micro and macronodules, confluent nodules, and a small PMF lesion. Mild focal, scar and paraseptal emphysema is present.

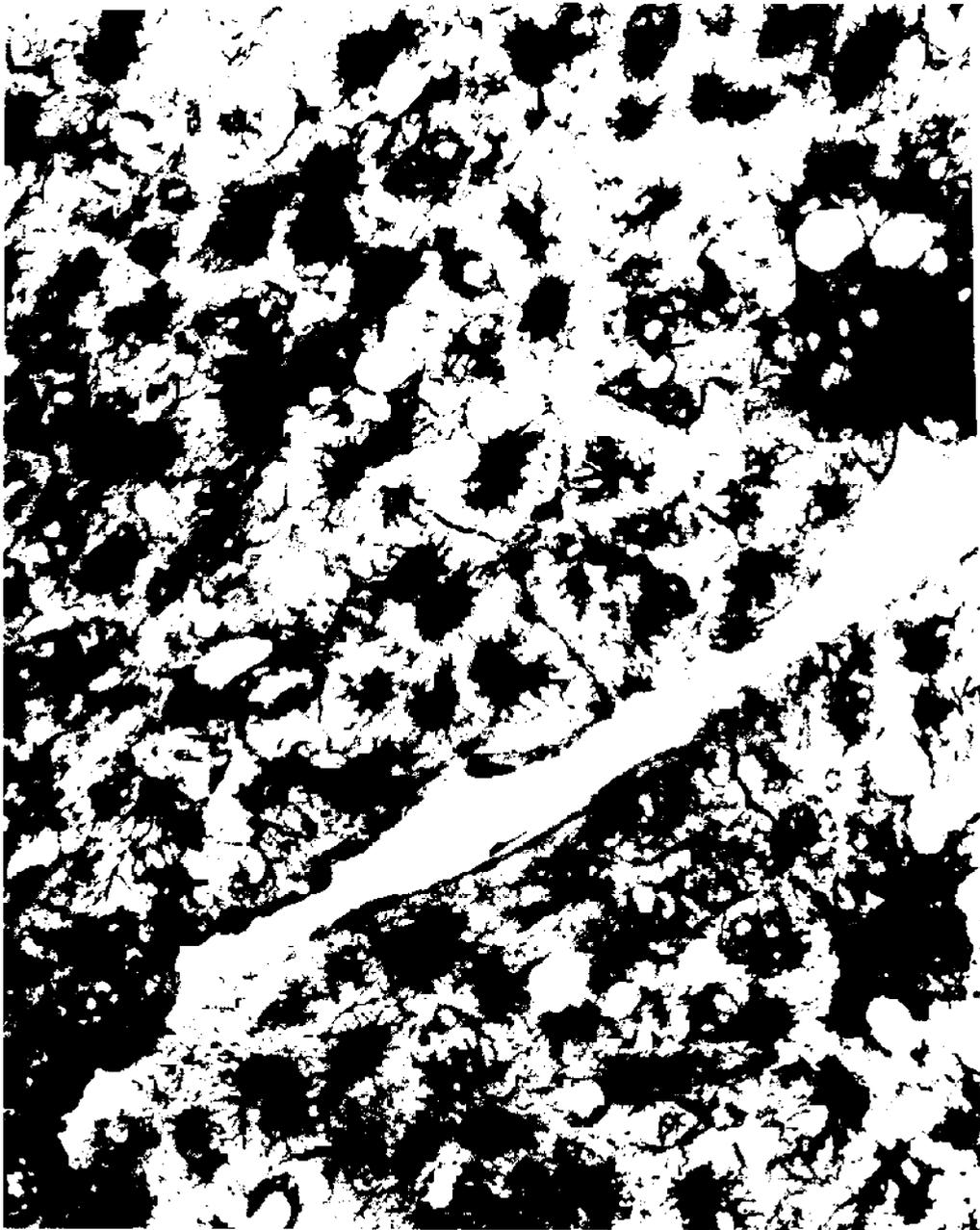


Figure II-27B. Close-up of micronodules and macules.



Figure II-28. Micronodule, composed of macrophages, dust and collagen. Hematoxylin and eosin $\times 250$.



Figure II-29. Silicotic nodule in the lungs of a coal worker. The nodule has a hyalinized center with concentrically arranged collagen fibers. The majority of the coal dust is at the periphery of the lesion. Hamatoxylin and eosin \times 150.

They may cross interlobar fissures and often involve the pleura, when firm adhesions to the chest wall develop. Despite the name PMF, the lesions may or may not progress once exposure to dust has ceased, and certainly with a minimum size of 1 cm, are not necessarily massive. Truly massive lesions which replace more than a whole lobe do, however, occur. The cut surface of a PMF lesion presents a homogeneous black appearance. The texture of PMF is rubbery rather than gritty or hard when cut. The margins of the lesions may be smooth or have fibrous prolongations into the surrounding tissue. Emphysematous change is common in the lung around a PMF lesion, but occasional lungs show remarkably little emphysema even in the presence of large PMF lesions. The center of the lesion of PMF may have cavities containing opaque black liquid. Histologically, the periphery is composed of irregular reticulin and collagen interspersed with black pigment (Figure II-30). Moving away from the edge, recognizable collagen becomes more scanty and amorphous material containing coal dust is seen. This material has been found to contain principally an insoluble protein of unknown origin, calcium phosphate, and coal dust (173). Blood vessels and airways transversing the lesion are destroyed.

There have been several hypotheses which attempt to explain the mechanisms involved in the generation of progressive massive fibrosis. These have involved the role of tuberculosis, of silica, of immunologic factors, and of genetic predispositions. None of these hypothesis is entirely satisfactory and the mechanisms involved are still not fully understood.

Studies of coal miners, particularly in South Wales, revealed a strong association between tuberculosis and progressive massive fibrosis. Often the infection could only be diagnosed by examination of tissue at autopsy and in life the prevalence of sputum samples positive for *Mycobacterium tuberculosis* was much lower. Thus Rivers et al. found only 1.1% of positive sputa in miners with CWP as opposed to an isolation rate of 29% from autopsy material taken from 153 miners with coal workers' pneumoconiosis (149). The isolation rate for miners with PMF was 35% as opposed to 11% of those with simple CWP.

In experimental studies, Zaidi et al. showed that administration of coal mine dust and tuber-

cle bacilli of low virulence resulted in massive fibrosis of the lungs in guinea pigs while neither alone produced this effect (176). This observation and the demonstrated association of tuberculous infection and PMF led to the hypothesis that PMF resulted from modification of the tissue response to coal dust by the infection. Several studies indicate that the development of PMF from simple CWP is not due to tuberculous infection. In a long-term study it was shown that decreasing the incidence of tuberculosis in a mining community did not result in a decrease in the attack rate of PMF (20)(24). Anti-mycobacterial chemotherapy was shown not to influence the course of early complicated CWP and some lesions progressed when not exposed to coal dust and while receiving chemotherapy (8). Thus, though associated in the past, tuberculosis does not have a clear etiologic relationship with PMF.

Because silica is a well-recognized fibrogenic agent, some researchers have suggested that silica in coal mine dust is responsible for the development of PMF. Evidence to support this hypothesis is limited and the occurrence of PMF in carbon electrode workers (174) and in coal trimmers who are exposed only to coal dust rather than coal mine dust (47) would support the view that silica is not necessarily involved. Comparison of the silica content of the lesions of PMF with that found in the rest of the lung did not show significant differences (129). Pratt criticized this conclusion because the silica concentration was related to tissue dry weight (141). He explained that when using this method of expressing results, the dry weight of tissue would increase because of tissue changes and, therefore, the concentration of silica expressed in milligrams silica per gram tissue would give a falsely low expression of true silica content. He was able to recalculate the data of Nagelschmidt et al. and by expressing the results as silica per whole lung, assuming that the lung was either wholly PMF or wholly non-PMF, showed that the silica content of PMF tissue was significantly higher than "the rest." The difference was of the order of twice. While this reopens the question of the role of silica in PMF, it certainly does not answer it.

Experimental animal studies have not been very helpful. Administration of coal dust with varying concentrations of silica to rats has shown little fibrosis with up to 10% of added silica



Figure II-30. Section from center of PMF lesion showing masses of black pigment embedded in bundles of haphazardly arranged collagen fibers. A cavity containing free dust and cholesterol crystals is seen at bottom right. Hematoxylin and eosin $\times 150$.

(153). Martin et al. carried out studies for a longer period of time and showed that after 18 months exposure, 5% quartz plus coal dust was about three times more active in generating fibrosis than coal dust alone (102). Intratracheal injection of coal mine dust obtained from the lungs of deceased miners containing 0.7% and 1.6% quartz also produced significantly more fibrosis after 18 months than demineralized dust (84). These studies show that the silica in coal mine dust is fibrogenic but its fibrogenic potential is mitigated (suppressed) by other minerals within the coal mine dust. The relationship of these experimental studies to pathogenesis of PMF is, however, obscure as the lesions induced more closely resemble the nodular lesions of simple CWP rather than those of PMF. Thus they support the role of silica in the generation of nodular lesions of CWP but do not help in understanding the mechanism involved in the development of PMF.

The association between rheumatoid arthritis and complicated pneumoconiosis was first noted by Caplan (15). The lesions—Caplan's lesions—could usually be differentiated from typical PMF on radiologic examination and were histologically different. However, because of this observation, the possible role of immunologic phenomena in the generation of PMF attracted some research. Miners with PMF were found to have a higher prevalence of circulating rheumatoid factor than those with simple pneumoconiosis. Rheumatoid factor was found in plasma cells present in the walls of blood vessels in relation to the PMF lesions (172). This was not an all or nothing situation: they found tissue rheumatoid factor in 20% of simple pneumoconiosis lesions as opposed to 67% of PMF lesions with histologic vasculitis. Rheumatoid factor was found in only 19% of lungs with PMF without histologic vasculitis, suggesting perhaps there were two variants of PMF, one being an atypical Caplan's syndrome. The association of circulating rheumatoid factor with complicated pneumoconiosis was not confirmed in a study carried out in Pennsylvania and West Virginia miners although a high prevalence of antinuclear antibody was observed (95). Antibodies reactive with insoluble lung antigens have been suggested as possible modifiers of the tissue response to coal dust (13). Such antibodies, possibly reactive with either collagen or reticulin, have been

demonstrated in the sera of a limited number of miners; however, there is no clear evidence on which to base an etiologic rôle in PMF.

The possibility that genetically determined mechanisms of tissue response to coal dust were involved in complicated CWP was investigated by comparing the frequencies of HLA histocompatibility antigen in miners with simple, complicated and with no pneumoconiosis (56). An association between HLA-1 and resistance to the development of both simple and complicated CWP was suggested. An association between resistance to the development of PMF and antigen W18 was also suggested but further work has not supported this observation (57).

The mechanism whereby progressive massive fibrosis develops from simple pneumoconiosis is thus still not known. It is possible that PMF is not a single entity and that multiple mechanisms are involved.

As already noted, Caplan's lesions is another possible diagnosis for a nodular radiological opacity in a coal miner's chest x-ray. The lesions are described as well-defined, rounded nodular masses 0.3 cm to 5 cm in diameter and usually situated more peripherally than other nodular lesions of CWP. Most commonly described in European miners, they appear to be relatively rare in the United States (10). Histologic description is provided by the studies of Gough et al. (48). Caplan's lesions are round or oval and may contain cavities. They characteristically show a concentric arrangement of lighter and darker layers. The pale areas may contain clefts and calcification and are more common than in other lesions of CWP. Pallasading fibroblasts, characteristic of many rheumatoid lesions, may be seen but are not prominent. There is characteristically a peripheral zone of active inflammation and vasculitis of local blood vessels. These histological features do not involve all pneumoconiotic lesions in a single lung and typical non-Caplan's lesions may be present side-by-side with typical Caplan's lesions. This indicates that local as well as systemic factors play a part in the generation of the lesion.

Emphysema, i.e., the enlargement of air-spaces distal to the terminal bronchiole, is a common finding in the lungs of deceased coal miners. In any nonminer population studied, emphysema of all types will also be found. A classification of emphysema is provided by the re-



Figure II-31. 74-year-old coal miner who worked 27 years underground as a loader, smoked 20 cigarettes a day for 40 years. Whole lung section shows an area of PMF in the upper lobe set against a background of macular and nodular lesions of simple COPD. The lung also shows moderately severe emphysema and enlarged, deeply pigmented, peribronchial lymph nodes.

port of CIBA guest symposium (18). Only two types of emphysema can be definitely (pathologically) related to the inhalation of coal dust. These are the focal emphysema associated with the coal macule and scar emphysema related to the nodular lesions (Figure II-31). Focal emphysema usually involves only a small portion of the proximal part of the acinus and its limited extent suggests that it has little functional significance. More extensive, destructive, centri-acinar emphysema is seen in a certain proportion of miners' lungs (154). These miners are usually cigarette smokers and it is difficult in an individual case to determine the relative importance of coal dust and cigarette smoke in the pathogenesis of these lesions. However, a recent study of coal miners with pneumoconiosis suggests that centrilobular emphysema may play a more important role in coal miners' lung impairment than previously appreciated (100). Although the numbers were viewed as too small to draw definite conclusions, smoking and nonsmoking miners were found to have similar degrees of centrilobular emphysema; before death, smokers were found to have lower lung function which the authors suggested was probably attributable to airway changes. The extent of the scar emphysema associated with nodules and PMF is highly variable. This suggests either other extraneous factors or individual variations in response are involved in its generation.

Chronic bronchitis, characterized by hypertrophy and hyperplasia of the bronchial mucous glands and goblet cell metaplasia of the small airways, is found in some coal miners' lungs. In general populations, these changes are associated with cigarette smoking. There are currently inadequate pathological data to relate the histologic changes of chronic bronchitis and coal dust inhalation; the entity "industrial bronchitis" is defined only by epidemiologic studies.

CLINICAL DESCRIPTION

Signs and Symptoms

The signs and symptoms of coal workers' pneumoconiosis (CWP) are the same as those which may occur with common nonoccupational lung diseases and are not, therefore, pathognomonic. One must rely on epidemiological studies to help determine to what extent clinical findings and pulmonary function test abnormalities can be attributed to coal mine dust exposure, and in

an individual case (particularly if a smoker) this determination can be difficult. A detailed history and physical, looking for other treatable conditions such as asthma or congestive heart failure, are mandatory.

If one accepts a strict radiologic or pathologic definition of CWP in the absence of other lung disease, most authorities would agree that simple CWP *per se* causes few, if any, signs or symptoms (124)(137). However, there is evidence that coal mining exposure is a risk factor in chronic bronchitis and emphysema. Chronic bronchitis is defined as persistent cough and phlegm production, and emphysema, if marked, is associated with significant airways obstruction, dyspnea, and disability.

While results of some research questioned that causal relationship between coal mining and chronic bronchitis, more recent work has validated this association (see Epidemiology). Nonsmoking miners may show an increased prevalence of cough and phlegm production, but it is not known whether this industrial bronchitis can produce airways obstruction of a degree sufficient to cause dyspnea. Indeed, there is some evidence to suggest that even in smokers, chronic mucus hypersecretion *per se* plays little role in the development of chronic airflow obstruction (41). In working miners, studies by Hankinson et al. show small, but statistically significant spirometric differences between bronchitic and non-bronchitic groups, similar in magnitude to the smoking effect at larger lung volumes (52)(53).

It is controversial whether simple CWP or coal mining exposure causes disabling emphysema. The main studies supporting this concept come from one British group (96-98)(154). From their pathological studies the authors conclude that in their study populations, CWP usually caused progressive impairment of ventilation and that in these cases the presence of emphysema was found to be a more important determinant of this impairment than the radiologic category of simple CWP. The later study found substantial ventilatory impairment in a group of legally disabled miners including those with simple CWP. Several criticisms have been made of these papers, including a possible selection bias by studying miners who had been certified as disabled, inclusion of cases with progressive massive fibrosis (PMF), and a lack of correlation between pulmonary function decrement and x-ray category (45)(123)(134). A recent paper

by Lyons and colleagues has again reported that centrilobular emphysema is as common among nonsmoking miners as smoking miners (100). The authors added that the number of cases was small, making definite interpretation of the role of emphysema in CWP and among coal miners still uncertain.

There is, however, general agreement that complicated CWP (PMF) frequently produces substantial symptomatology and impairment, often associated with emphysema. Particularly in Categories B and C of PMF, cough, sputum production, and some degree of dyspnea are common. Melanoptysis, the often dramatic production of several ounces of black inky sputum from a ruptured lesion, can be considered the only specific, although somewhat unusual, clinical sign of CWP. On physical exam one may find evidence of collapse and consolidation as well as the decreased breath sounds, prolonged expiration, and adventitial sounds found in obstructive airways disease. In severe cases, signs of pulmonary hypertension, right ventricular hypertrophy, and congestive failure (cor pulmonale) may be present. PMF may also produce signs of restrictive pulmonary disease.

For proper medical management as well as correct disability evaluation, it is important to know which signs and symptoms should not be attributed to CWP or coal mining exposure. Thus chills, fever, night sweats, anorexia, weight loss, and usually finger clubbing require other explanations. Chest pain or hemoptysis, particularly in simple CWP, should prompt further diagnostic evaluation, just as it would in a non-miner.

Natural History

Coal workers' pneumoconiosis takes years to develop. In one large British study of face-workers by Jacobsen et al., only 7% of those starting with 1971 ILO U/C x-ray classification of 0/- or 0/0 (i.e., no pneumoconiosis) had any radiographic progression over a 10-year period (74). Another large study by Reisner from West Germany gave similar results (148); both found the risk of pneumoconiosis to be highly correlated with the amount of dust exposure. Importantly, Jacobsen's study found that CWP in miners with early dust retention (Category 0/1 or 1/0) was more likely to progress than the CWP classified as Category 0/0. In other words, in

miners who develop the disease sooner, it progresses more rapidly. Thus the chance of radiologic progression over 10 years at a mean dust concentration of 2 mg/M³ is essentially zero for a miner with x-ray Category 0/0, but is 20% for one with Category 1/0. Similar differences were found at all levels of dust exposure during the 10-year study; this suggests either a harmful effect from early pneumoconiosis predisposing to more rapid dust accumulation or variability in individual susceptibility to CWP.

The attack rate of progressive massive fibrosis (PMF) has been well-studied in over 100,000 British coal miners by McIntock et al. (106). Calculations from their data show a PMF attack rate of approximately 0%, 1%, 11% and 21% over an eight-year period for simple pneumoconiosis Category 0, 1, 2, and 3, respectively. Rephrased, this means that 1.5% of coal miners with 1971 ILO U/C Category 2 or more simple pneumoconiosis would develop progressive massive fibrosis per year. Independent of this increased attack rate of PMF with increasing simple CWP category, the authors also found an increased attack rate with more rapid progression of simple CWP. This again raises the question of increased individual susceptibility to the effects of coal dust. It is not known whether the given risks of contracting PMF continue indefinitely. Particularly in applying these data to the U.S. mining experience, one should note that substantial regional differences were noted in the above studies which could not be fully explained by the various factors mentioned. In part these differences may be explained by the type of coal mined, dust concentration, and free silica level. A recent report suggests a significant role of free silica content on the attack rate of PMF (72).

While radiologic regression of both simple and complicated CWP can be seen, this apparent reversibility is uncommon and may well represent observer variability in reading the radiographs. There is no doubt that the lesions of complicated pneumoconiosis may contract, but this clearly should not be viewed as clinical improvement. Little evidence exists to suggest any significant resolution of pulmonary impairment caused by CWP. In contrast, it is generally acknowledged that PMF may develop several years after employment ceases, and that once initiated, the process may progress whether exposure continues or not (116). In fact, Cochrane et al. could find no effect of continued dust exposure on the pro-

gression of PMF (25). He analyzed the radiographs of miners and ex-miners with PMF over an eight-year period and found that comparing the measured area of involvement on serial PA chest x-rays gave a more sensitive indicator of change than routine clinical readings. Using the former method, 13% of 579 individuals with all stages of PMF showed either no change or improvement in their x-rays over the eight years, and 87% progressed. Looking at the 341 cases starting with less than 20 sq cm of involved area (i.e., Category A), 45% showed progression over the eight year study period. Importantly, Cochrane also showed that the progression was greater in the younger population. Thus, of the group starting with Category A, 69% of those less than age 45 showed progression while only 32% of the older cases progressed.

Alternatively, with regard to the progression of simple CWP, the work of Jacobsen et al. (74), Reisner (148), and the close correlation between the radiographic category and coal content of the lungs (17) all indicate that stopping coal dust exposure should prevent further progression. Hence, the rationale for transferring miners with simple CWP to low dust areas.

Finally, it is important to note that a miner's x-ray category reflects his dust exposure over his entire working life and that with the new and lower dust standards, the natural history of CWP is changing. The data of Jacobsen et al. indicate that the probability of developing category 2/1 or higher simple CWP after 35 years exposure to a mean dust concentration of 2 mg/ M³ is near zero (74). Thus, in the present generation of beginning U.S. miners, advanced simple CWP and more importantly, potentially disabling PMF, should become a rare occurrence.

Laboratory Investigations

Pulmonary Function Tests

The comments made regarding the non-specificity of the respiratory signs and symptoms in coal miners apply equally well to pulmonary function abnormalities. Pulmonary function tests cannot diagnose CWP, but can detect physiologic impairment from whatever cause. Therefore, the physiologic evaluation of a miner with symptoms referable to the chest would be the same as for a nonminer.

Simple CWP

While conflicting series exist, several U.S.

studies show that miners have lower ventilatory capacity compared to controls or predicted normal (60)(87)(139). This impairment, although significant, has not been large. Thus, in a large nationwide study of working U.S. bituminous miners, the mean FEV₁, FVC, and FEV₁/FVC ratio were normal or more than 90% of predicted in all categories of simple CWP (121). British and other studies also show conflicting results, most showing no effect or a small decline of function with simple pneumoconiosis (5)(62).

It is also important to note that while an occasional study describes decreasing values in Category 3 (65)(151), the majority find no correlation between the radiographic profusion of simple CWP and ventilatory capacity (23)(121)(126)(127)(139)(146). This lack of correlation is consistent with the involvement of small airways as was shown in the "Pathology" section. These peripheral airways normally contribute only 10-15% to the total airway resistance and thus represent a "quiet" zone of the lungs (107). That is, they must sustain substantial damage before changes will be detected by the relatively insensitive standard spirometric tests such as FEV₁ and FVC. In the case of CWP, this concept of small airways involvement is supported by the analysis of Bates (9) and several studies. Morgan, for example, found small increases in residual volume even in miners with a normal FEV₁ and suggested this represented either focal emphysema or, more likely, increased resistance to flow in the small airway (120). The frequency dependence of dynamic compliance found by Seaton in miners with simple CWP, but without significant large airways obstruction, also suggest small airways disease (156).

While it seems that simple CWP *per se* causes mild small airways disease, coal mining exposure may also cause chronic industrial bronchitis as discussed elsewhere. In a large-scale study of working U.S. miners, Hankinson et al. found chronic bronchitis to be associated with small decreases in flow at high lung volumes during a forced expiratory maneuver (52)(53). This, together with a normal total lung capacity, was interpreted as indicating large airways obstruction due to industrial bronchitis without emphysema. It is apparent, therefore, that the reduction in ventilatory capacity sometimes seen in miners with simple CWP can in part be explained by this concept of industrial bronchitis.

Most U.S. and foreign studies of the dif-

fusing capacity in simple CWP have shown normal or slightly decreased values (30)(31)(82)(157)(162). The last three references also noted that the diffusing capacity and, in Cote's studies, several other tests of lung function were lower in those with the "p" type of opacity compared to those with "q" opacity. The explanation for these interesting differences remains unclear.

Studies of gas exchange in U.S. miners report varying results. Lapp and Seaton studied 51 symptomatic miners who had FEV₁/FVC ratio greater than 70% and found an increased physiological dead space to tidal volume ratio (VD/VT) as had been shown in previous studies (89). The VD/VT returned to normal or near normal with exercise in all simple CWP categories except in the combined Category 3 plus Category A of PMF. The alveolar-arterial gradient for oxygen ((A-a)O₂) was similarly slightly abnormal or in the high normal range. Arterial oxygen saturations were in the low normal range. Rasmussen et al. found similar values for VD/VT, ((A-a)O₂) and arterial oxygen saturation in their series of 192 symptomatic miners, including 158 with simple CWP (146). They found marked hyperventilation and impairment of oxygen transfer with exercise, however, even in those miners with normal spirometry. These results, together with their other findings, including frequent pulmonary hypertension, were interpreted as indicating significant pulmonary vascular involvement and ventilation/perfusion abnormalities, even in the absence of chronic airways obstruction. Rasmussen, in a larger study, reached similar conclusions (145) although both his methods and interpretation have been challenged (43). One can conclude that while gas exchange abnormalities are not uncommon in symptomatic miners with simple CWP, it is not clear that they are of great enough magnitude to explain dyspnea.

The lung mechanics in working U.S. coal miners have been studied in a series of articles by Lapp and Seaton (88), Seaton et al. (156), and Morgan et al. (125). These authors found normal or slightly reduced values for static lung compliance and pulmonary recoil pressure in simple CWP. Frequency dependence of dynamic compliance, often considered a sensitive indicator of small airways disease, was found in 17 of 25 cases of Category 2 and 3 simple CWP, while Category 1 showed minimal decrements and Category 0 showed no significant change in

dynamic compliance with increasing respiratory frequency.

Rasmussen's group studied systolic pulmonary artery pressures in 26 symptomatic miners who had no or mild obstruction and found elevated pressures in 7 at rest, and in 18 during exercise (146). In contrast, studies using the more reliable mean pulmonary artery pressure have found substantial pulmonary hypertension to be quite unusual in CWP without airways obstruction (86)(90)(133)(162). Interestingly, Lapp's group found the "p" type of opacity to be more associated with high pulmonary artery pressures. This group also performed lung scans in miners and found perfusion defects in 9 of 21 patients with simple CWP (155). However, in only two cases, both with Category 3 profusion and one probably with silicosis, were the scan defects thought to be due to pneumoconiosis. Abnormalities such as old tuberculosis were found to explain the scan defects in the remaining seven patients.

In discussing simple CWP, it should be noted that anthracite coal seems to cause greater impairment for a given x-ray category than does bituminous (121)(127), although the reason for this is not completely known.

Complicated CWP (PMF)

In contrast to simple CWP, PMF is often associated with abnormalities in most pulmonary function tests and these are generally correlated with the extent of lung involvement. However, this correlation is found primarily in the higher categories of PMF; indeed, several studies have shown pulmonary function to be near normal in Category A (23)(126). With Categories B and C of PMF, one frequently finds a marked reduction in ventilatory function, low diffusing capacity, and gas exchange abnormalities (89). Pulmonary hypertension and cor pulmonale may be present even without severe obstruction. Respiratory failure is not uncommon in severe cases. Depending on the relative proportions of emphysema and fibrosis present, pulmonary compliance may be either increased or decreased. There are few large studies in this area; the available data is reviewed by Marek (101).

Radiological Studies

The chest radiograph is the only way of confirming the presence of CWP in life other than lung biopsy, which is rarely, if ever, indicated.

In general, if the history of exposure and the chest radiograph are consistent with the diagnosis of CWP and any signs and symptoms present are compatible with this condition, no other diagnostic procedures are necessary.

The typical radiographic opacities seen in simple CWP are rounded opacities of the "q" size and shape, although "p" and less commonly "r" opacities are seen (Figures II-32-II-36). A mixed pattern of rounded and irregular opacities are sometimes found. The lesions tend to predominate in the upper zones of the lungs in the earlier stages (2)(137). Amandus et al., found that approximately 6% of working U.S. coal miners showed small irregular opacities either alone or with rounded opacities on their radiographs (1). The irregular lesions were correlated with cigarette smoking, as well as bronchitis, age, and years worked underground. Lyons et al. have shown that these lesions (unlike rounded opacities) also correlate with the extent of emphysema and the impairment of FEV₁ (99).

The lesions of PMF may vary greatly in shape as well as size, and may be single, multiple, unilateral, or bilateral (Figure II-37). They usually predominate in the upper lung zones but can occur anywhere; they may cavitate and (rarely) calcify. Typically, they are multiple irregular masses that tend to migrate towards the hila by contraction of fibrotic tissue. PMF usually develops on the background of Category 2 or 3 simple CWP, although traction by the conglomerate masses may overdistend the remaining tissue, rendering the simple CWP less evident on x-ray. Thus previous radiographs are often important in supporting the diagnosis of PMF.

It is important to note that none of the described radiographic features of CWP is pathognomonic. In addition, certain findings should cause one to question this diagnosis. These would include noncalcified hilar or mediastinal adenopathy and pleural effusion. Caplan's syndrome—the occurrence of multiple pulmonary nodules in a miner who usually has rheumatoid arthritis with subcutaneous rheumatoid nodules—is mentioned as the one variant of CWP which progresses rapidly. These lesions resemble necrobiotic rheumatoid nodules pathologically and may appear over a period of weeks as opposed to years for PMF.

Lung Biopsy

While this procedure can usually confirm a diagnosis of CWP (see Pathology section, page 353), it is rarely medically indicated. The main clinical setting in which a biopsy may be necessary is when a solitary mass lesion is seen on the chest radiograph. Here one may not be able to distinguish carcinoma (or other mass lesion) from PMF, and biopsy may therefore be indicated for proper patient management.

Other Tests

While much interesting research has been done in the area of other laboratory (particularly immunological) tests, at present no laboratory test is diagnostic for CWP, and none can accurately predict which miner will develop the disease.

Treatment

No effective treatment of CWP is known. While previous animal studies have suggested polyvinylpyridine-N-oxide (PVNO) is effective, although less so than in silicosis, a recent controlled long-term trial by Weller in monkeys with simulated CWP showed no beneficial effect of the chemical (175). At present the clinician's role in respiratory treatment is limited to managing the complications of CWP or the incidental cardiopulmonary diseases which afflict the miner, to providing guidance as to further occupational exposure, and to strongly advise against smoking.

CWP and Tuberculosis

Tuberculosis plays a doubtful role in producing PMF, as discussed in "Pathology." While there is little evidence indicating any increased risk of contracting tuberculosis in CWP, some articles suggest that CWP affects the pathogenicity of the infection. These studies show antituberculosis chemotherapy to be less effective in the presence of CWP (11)(44)(143). While silicosis clearly predisposes to tuberculous disease which may then be poorly responsive to chemotherapy, it is unclear if the small amount of silica in coal mine dust causes a similar problem. Although standard antituberculosis chemotherapy should be adequate when *Mycobacterium tuberculosis* is identified in the sputum, some cases will have to be individualized (116). Thus, the clinical, bacteriologic and radiologic

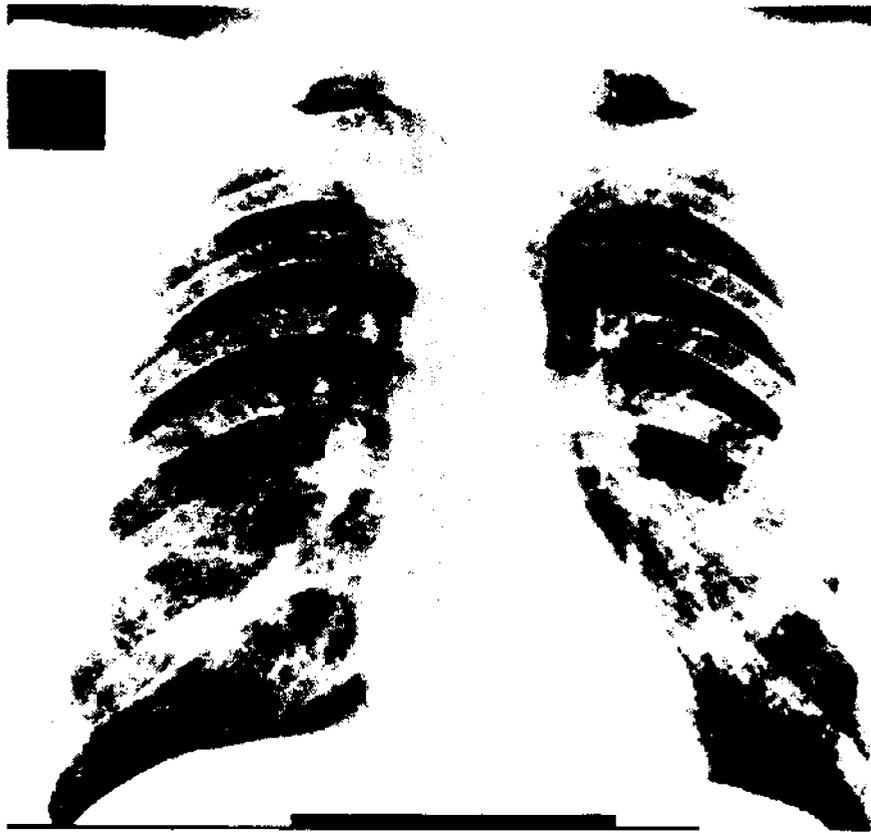


Figure II-32. Normal chest radiograph. Profusion category 0/0.

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response of miners with historical (roofbolters or drillers) or radiologic (eggshell calcifications) evidence of high silica exposure should be carefully followed. In this regard, Dubois et al. have found rifampin-combined chemotherapy to be effective in new and retreatment cases of TB in coal miners (37).

DIAGNOSTIC CRITERIA

The usual clinical criteria for diagnosing coal workers' pneumoconiosis are a documented history of substantial (usually at least ten years) exposure to coal dust and a chest radiograph consistent with the diagnosis (ILO 1980 Classification Profusion Category I or greater). The combination is not pathognomonic, and consideration must be given to other occupational as well as nonoccupational chest diseases. Usually with a history, physical exam, and old chest

x-rays, diseases which can present with a pattern mimicking simple CWP, such as miliary tuberculosis, histoplasmosis, or sarcoidosis are easily differentiated. Some other pneumoconioses, particularly silicosis, can present with an identical radiographic pattern. In such cases a lung biopsy is the only way to obtain a definitive diagnosis, but is not recommended as a substitute for a good occupational history.

Differentiating other diseases from complicated CWP is more difficult. The diagnostic possibilities may include tumor, tuberculosis, fungal diseases, and some vasculitic conditions. As in the case of simple CWP, a lung biopsy should yield a definitive diagnosis in clinically confusing cases; however, in most cases this procedure is not required for proper patient management.

A more complete list of the differential

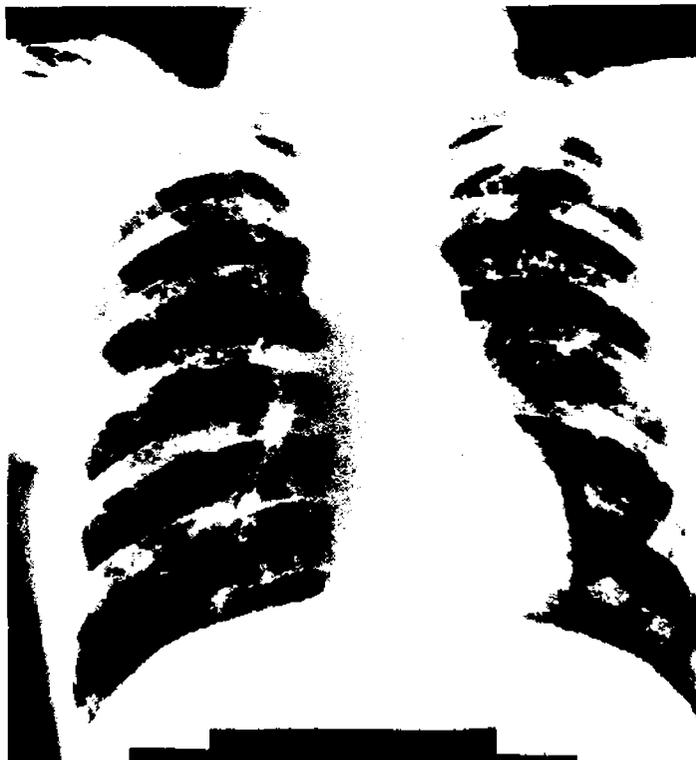


Figure II-33. Simple coal workers' pneumoconiosis. Profusion category 1/1. Size and shape r/r.

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diagnostic possibilities in CWP is presented in standard textbooks and in articles by Van Ordstrand (170) and Pendergrass et al. (140). Since the occupational history and chest radiograph are not pathognomonic, there is always room for some debate regarding the diagnosis in coal workers' pneumoconiosis. The Department of Labor has recently established standards for the assessment of lung impairment and disability under the Black Lung Benefits Reform Act of 1977 (167). These guidelines, and the arguments for and against them, are contained in the preamble preceding these standards. It should be emphasized that these criteria were formulated to facilitate the processing of compensation cases and are not meant to substitute for a good clinical evaluation of any medical problem in a miner.

PREVENTION

As noted previously, the basic methods to prevent coal workers pneumoconiosis and associated airways disease were defined over a

century ago when the importance both of adequate mine ventilation and removal of affected miners was appreciated. With definition of the dose-response relationship between respirable coal mine dust and pneumoconiosis, new dust standards were quickly adopted in Great Britain and the United States. The U.S. dust standard was initially set at 3 mg/m³ to be reduced to 2 mg/m³ by 1973. As shown in Table II-23, the U.S. coal mining industry has made excellent progress in meeting the dust standard with over 90% of U.S. mining sections now in compliance. Smaller mines and long-wall operations, which are increasing in number, tend to have greater difficulty meeting the standard. Dust control has been achieved by attention to mine ventilation and assisted by the use of water spraying on the continuous miner (a mining machine).

Use of diesel powered mining equipment may offer safety advantages, but introduces possibly hazardous exposures (oxides of nitrogen and other irritating gases as well as carcinogens and mutagens) into the mining environment. The

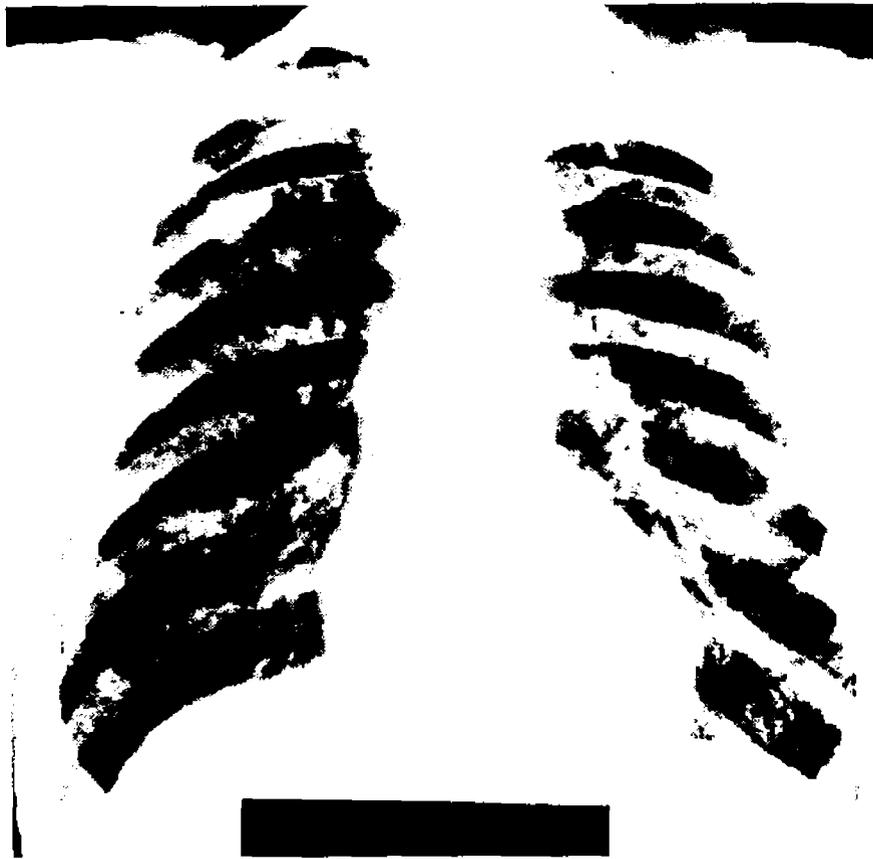


Figure II-34. Coal workers' pneumoconiosis. Profusion category 2/2. Size and shape p/p.

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extent of these exposures and their possible effects are not yet adequately defined. Although significant free silica concentrations in U.S. mines are usually relatively low, those who drill through siliceous overburdens may get high exposures to free silica and develop acute silicosis. Therefore, sampling for free silica in addition to respirable dust is always necessary.

Medical surveillance is the second important means to prevent disabling pneumoconiosis. The Federal Coal Mine Health and Safety Act of 1969 mandated pre-employment and periodic medical examinations be offered to underground coal miners through a program to be administered by NIOSH. The Act also provided that these examinations be paid for by the mine operator and that miners with evidence of coal workers' pneumoconiosis be given the opportunity to transfer to a low dust area ($1 \text{ mg}/\text{M}^3$ or lower) without loss in pay (transfer rights and rate retention). The National Coal Workers'

Health Surveillance Program was established in 1970 by NIOSH at its Appalachian Laboratory for Occupational Safety and Health (ALOSH). Under regulations adopted by NIOSH, medical examinations (occupational questionnaire and PA chest radiograph) are conducted by facilities (hospitals and clinics) certified by NIOSH and located throughout the coal fields (168). Qualified physicians ("A" Readers) located at the facilities interpret the radiograph for clinical pathology and for pneumoconiosis according to the 1980 ILO Classification scheme. Radiographs are then sent to ALOSH where they are coded and batched for a second reader ("B" Readers—those who have passed a NIOSH proficiency examination on interpretation of the pneumoconiosis). If "A" and "B" readers do not agree within one subcategory of the 1980 ILO Classification, further "B" readings are obtained until agreement is achieved. Miners with Category 1 profusion are judged to have evidence of pneu-



Figure II-35. Simple coal workers' pneumoconiosis. Profusion category 2/2. Size and shape q/q.

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moconiosis and are extended an option to transfer to a low dust area through a letter from the Administrator of MSHA. MSHA continues to follow miners who have exercised their option to ensure exposure to low dust levels.

Results of the third round of examinations of the National Coal Workers' Health Surveillance Programs are shown in Table II-24. The prevalence of CWP continues to slowly decline with most advanced simple CWP and PMF occurring among miners with more than twenty years underground. This, therefore, largely reflects previous higher dust exposures. Based on the British dose-response experience and current trends in dust control and medical surveillance findings, it appears that *advanced CWP per se* should become a relatively uncommon condition among U.S. coal miners.

Airways obstruction is now a much more important problem among coal miners than is pneumoconiosis. Because of the dose-response

relationship between coal mine dust exposure and decline in FEV₁, NIOSH has proposed that lung function testing be incorporated into the surveillance program. This has not yet been adopted and as a result, reasonably good prevalence and incidence estimates will continue to be available for CWP but not for lung impairment. However, based on available epidemiological information and current respirable coal mine dust levels, the contribution of dust exposure to decline in lung function should be reduced. Without a similar decrease in the consumption of cigarettes, cigarette smoking will assume an even larger role in causing airways obstruction among miners. Unfortunately, the dispute over the role of coal dust and smoking has polarized the miners and operators and, to an extent, the public health community, making it difficult to convince miners of the importance of cigarette smoking in the causality of their lung disease. This remains the area of greatest con-



Figure II-36. Simple coal workers' pneumoconiosis. Profusion category 3/3. Size and shape r/r.

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cern in prevention of respiratory disease of coal miners.

RESEARCH NEEDS

Despite the extensive research reviewed in the previous sections, a number of important questions remain partially or fully unresolved:

1. Pathological/epidemiological investigations on inflated lungs together with other clinical data and good occupational and smoking histories are needed to document the nature and extent of chronic bronchitis and the emphysemas among coal miners with and without simple CWP and PMF.
2. Prospective epidemiological studies of coal miners should continue with an emphasis on further defining dose-response relationships and risk factors relating to airways obstruction at low levels of coal mine dust exposure (under $2 \text{ mg}/\text{M}^3$).
3. Development of more sensitive and specific methods to detect dust deposition in the lung should continue to be a research priority.
4. Further refinement of epidemiological methods to reduce variability in testing miners should continue to be a research priority.
5. Cohort, case-control, and laboratory investigation is needed to resolve etiologic questions regarding the role of coal mine dust exposure and other potential risk factors in stomach cancer incidence.



Figure 11-37. Coal workers' pneumoconiosis—progressive massive fibrosis category C.

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6. Epidemiological and experimental assessment should be continued to clearly define whether diesel emissions pose a hazard to miners, and if so, the nature and extent of the health effects and measures which might be taken to mitigate or prevent such possible health effects.

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BERYLLIUM DISEASE

Nancy L. Sprince

INTRODUCTION

Acute and chronic beryllium disease is caused by exposure to beryllium compounds.

Acute beryllium disease, the acute response to inhaling toxic beryllium compounds, is defined as disease which lasts less than one year, occurs during exposure to beryllium, and includes any or all of the following: nasopharyngitis, tracheitis, bronchitis, pneumonitis, dermatitis, and conjunctivitis.

Chronic beryllium disease is caused by inhalation of beryllium, lasts longer than one year, and usually causes both systemic and pulmonary abnormalities.

A separate disease form is subcutaneous granulomas secondary to direct implantation of beryllium compounds in the skin.

The term berylliosis will not be used in this report, because confusion has resulted from that terminology. Hardy and Chamberlin have noted that the word berylliosis implies two false conclusions: beryl ore itself causes disease and beryllium disease is similar to dust diseases of the lung (the pneumoconioses) (8).

CAUSATIVE AGENTS

The experience of the Beryllium Case Registry since 1952 and the data from many published reports of beryllium disease occurring in workers, support the conclusion that beryllium metal and all forms of beryllium, excluding beryl ore, have been associated with disease in humans.

Stokinger concluded that "chronic respiratory disease has occurred in connection with almost every major type of beryllium manufacture and use" (26). More recently, Hamilton and Hardy summarized 22 years of data from the Beryllium Case Registry and concluded that beryllium metal and all beryllium compounds, except beryl ore, have caused disease (7). Previous studies have emphasized the difference in disease

potential between beryllium compounds associated with chronic or with acute disease. For acute disease, the more soluble beryllium compounds, including beryllium fluoride, beryllium sulfate, and ammonium beryllium fluoride, have been implicated as the cause of both upper and lower respiratory abnormalities. In addition, acute pneumonitis has been associated with beryllium oxide, carbide, oxyfluoride, hydroxide, and zinc beryllium silicate. For chronic beryllium disease, beryllium oxide, beryllium phosphors, and beryllium copper alloys have been implicated.

However, these categorizations have been confused by the fact that almost all beryllium operations can produce more than one form of airborne beryllium. Based on current knowledge, therefore, all beryllium compounds except beryl ore should be considered potentially harmful.

OCCUPATIONS AND INDUSTRIES USING BERYLLIUM

1. Mining*
2. Extraction of beryllium
3. Beryllium metallurgy
4. Production and use of beryllium alloys
 - a. Beryllium copper alloys—springs, diaphragms, electrical contacts, connectors in electronics and data processing equipment, bearings, gears, airplane engine parts, precision castings, molds, antispark tools, welding electrodes and fixtures
 - b. Beryllium nickel alloys—instrument diaphragms, high-temperature springs, matrices of diamond drill bits, fuel pumps, dies for shaping
 - c. Dental alloys—nickel, chromium, beryllium

*To date, no cases of beryllium disease have been identified from mining operations.

- d. Other alloys (including aluminum, magnesium, and platinum)
5. Computers
6. Beryllium ceramics manufacturing—crucibles, spark plugs, bricks, thermal coatings, rocket motor parts, nose cones
7. X-ray tube window manufacturing
8. Electronic equipment manufacturing
9. Nuclear reactor manufacturing
10. Atomic energy development and research
11. Guidance and navigation systems manufacturing (gyroscope housings)
12. Rocket parts, heat shields, instruments
13. Gas mantle manufacturing
14. Rocket fuel development research
15. Salvage of fluorescent and neon lamps
16. Nonferrous foundry products
17. Tool and die manufacturing

EPIDEMIOLOGY

Information concerning the occurrence and distribution of beryllium disease in populations exposed to this material is available from several sources. Studies of beryllium extraction and fluorescent lamp workers in the 1940's, analyses of neighborhood cases, studies of working populations exposed to beryllium after 1950, and Beryllium Case Registry data from over 890 cases of beryllium disease are major epidemiologic sources.

Beryllium disease prevalence data derived from working populations before 1950 are of limited value. Studies of workers exposed to beryllium prior to 1950 were concerned with exposures which were different in type and intensity from modern exposures. After 1950, beryllium disease cases decreased markedly in association with generally reduced beryllium air concentrations in the workplace. Therefore, information on disease prevalence derived from studies of extraction or alloy workers prior to 1950 is not comparable with that obtained after 1950 for the same operations. Another working group studied previously was fluorescent lamp production workers. Beryllium was discontinued from use for that purpose in 1950. All studies have been affected by the fact that beryllium disease may develop 20 to 25 years after the last known exposure to beryllium. To the author's knowledge, published reports of long-term

longitudinal follow-up of entire plant populations exposed before 1950 are not available. The high rate of worker turnover during World War II frequently limited exact information about the total population at risk from exposure in many studies. Therefore, limited conclusions can be drawn from studies published in 1950 and reviewed by Tepper, et al., citing prevalence rates (mainly, acute beryllium disease) of 0.3% in the extraction industries, 2% in the beryllium copper alloy industry, and 3% in a fluorescent lamp plant (27).

Another study cited by Tepper et al. reported on the occurrence of beryllium disease in a total of 1,850 exposed persons in an extraction plant (27). Employees' health records were analyzed over an eight-year time period from 1940 to 1948. Results showed that 7% of the workers developed acute beryllium disease and 0.9% chronic disease. In another group of 191 workers in a research facility using beryllium, the rates for acute and chronic disease during that 8-year period were 3.7% and 4.2% respectively.

Beryllium disease has been reported in patients with no known occupational exposure to beryllium, but who lived near a plant or industry utilizing beryllium. A report by Eisenbud et al. described 11 patients with chronic beryllium disease of nonoccupational etiology living in the vicinity of a beryllium extraction plant (4). Ten of 11 cases lived within 0.75 miles of the plant, suggesting community exposure from plant discharges into the air. Results of air concentration measurements of beryllium at locations surrounding the plant provided information for the community air beryllium threshold limit value of $0.01\mu\text{m}/\text{m}$. Tepper et al. reviewed 47 cases of neighborhood chronic beryllium disease listed with the Beryllium Case Registry and found that 24 had been exposed to beryllium-contaminated clothing at home, 13 had only lived near a plant utilizing beryllium, 8 had both lived near a plant and had exposure to contaminated clothing, and in 2 cases the exposure source remained unknown (27). These data suggest that both contaminated work clothes and community pollution with beryllium-containing air from stack discharges account for neighborhood cases of chronic beryllium disease.

Recent data from the Beryllium Case Registry indicate the prevalence of neighborhood cases has decreased since 1949 due to control measures. Of 672 cases exposed to beryllium

before 1949, 11% were reported by Hasan and Kazemi as neighborhood cases in contrast to 3% in 36 cases exposed after 1949 (10). Of the 55 cases admitted to the Beryllium Case Registry from 1973 to 1977 and reported by Sprince and Kazemi, only one was a neighborhood case (22).

Current information concerning prevalence and distribution of chronic beryllium disease in working populations exposed after 1950 is available from several studies. Kanarek et al. reported the results of a medical and environmental survey at one beryllium extraction and processing plant in Pennsylvania (12). They found that 14% of 214 employees surveyed had the radiographic abnormality indicative of interstitial pulmonary disease and 5% had both interstitial disease on x-ray and hypoxemia ($P_{aO_2} < 80$ mmHg), probably secondary to beryllium disease. These abnormalities were found in association with some peak air concentrations of beryllium in that workplace exceeding 50 times the accepted peak threshold limit value (TLV) of $25 \mu\text{g}/\text{m}^3$. Four workers from this plant were admitted to the Beryllium Case Registry, having met the criteria for the diagnosis of chronic beryllium disease.

Follow-up study at that plant three years later reported by Sprince et al. revealed that peak air concentrations of beryllium were reduced to below $25 \mu\text{g}/\text{m}^3$ throughout the plant and that improvements in hypoxemia and interstitial disease (radiographically) occurred in some workers who had continued to work at the plant and had received no medical treatment (21).

A 1977 survey in a beryllium-copper alloy production plant in Pennsylvania (unpublished data) revealed that, of 305 workers surveyed, 3 workers (1%) met diagnostic criteria for chronic beryllium disease and were admitted to the Beryllium Case Registry. A total of 8 workers—2.6% of the work force surveyed—were found to have interstitial disease on x-ray, probably related to beryllium inhalation.

A study from Britain by Coates et al. reported that 3 of approximately 130 beryllium production workers followed for 25 years (1952-1977) developed chronic beryllium disease, and 2 others had an episode of acute pneumonitis secondary to beryllium exposure (2).

Although these studies point to a low prevalence of chronic beryllium disease in current working populations, the true prevalence of beryllium disease is most likely higher. Retired

employees, patients lost to medical follow-up, and individuals who develop beryllium disease after the well-documented (possible) latent period of up to 25 years between exposure and onset of disease, are not included in results obtained from the active work force.

The other source of information is the Beryllium Case Registry (BCR) which was established at the Massachusetts General Hospital in 1952 by Dr. Harriet L. Hardy. The main purpose of the BCR was to collect medical information and exposure data from patients in the United States with beryllium disease, to study the course and complications of this disease, and to establish criteria for the diagnosis of beryllium disease. The BCR has continued those studies and currently has on file 892 cases of patients with beryllium disease: 636 with chronic disease, 212 with acute disease, and 44 who developed chronic disease after having one or more episodes of acute disease. Of the total, 408 are known to be dead, 361 are known to be alive, and in 123 cases, the status was unknown at last follow-up in 1978. Sprince and Kazemi have reported approximately 10 to 12 new cases admitted to the BCR annually for the past five years, 40% of whom had initial exposure to beryllium after 1950 (20). Sources of exposure of recent cases are summarized in Table II-25.

Although 892 represents the total number of cases reported to the BCR from 1952 to 1978, this number is most likely an underestimate of actual disease prevalence because 1) physicians unfamiliar with this uncommon disease frequently do not consider it as a diagnostic possibility; 2) recognized difficulty exists in differentiating beryllium disease from other pulmonary granulomatous diseases, especially sarcoidosis; and 3) large numbers of patients with recognized beryllium disease have not been reported to the BCR.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk for beryllium disease in the workplace includes workers engaged in all operations producing or using beryllium and its compounds, excluding beryl ore mining. Exposures also occur in operations which involve melting, casting, grinding, machining, and drilling of beryllium-containing products. A U.S. Public Health Service Survey in 1970 estimated that at least 30,000 working people could have potential exposure to beryllium by inhalation.

Table II-25
BERYLLIUM CASE REGISTRY—
CASE ENTRIES 1973-1978
SOURCE OF EXPOSURE

1. Extraction and smelting	7
2. Beryllium metal production	30
A. alloys	18
B. ceramics	3
C. x-ray tubes	2
D. research (atomic)	6
E. vacuum tube	1
3. Fluorescent tube production	17
4. Neon tube production	1
5. Neighborhood cases	1
6. Unknown	4
	60*

*Of the 60 total cases, 43 were men, 17 women. Initial exposure to beryllium occurred before 1950 in 37 cases, after 1950 in 23 cases.

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However, the recent National Occupational Hazard Survey, looking at exposure to beryllium and beryllium oxide, estimated that 21,233 people in 2,019 plants had potential exposure to beryllium and 855,542 people in 93,132 plants had potential exposure to beryllium oxide. Since results of these two surveys are widely divergent, further investigations are required to determine which is accurate.

The scientific basis for an estimate of disease prevalence has been summarized in the preceding section, *Epidemiology*, page 386.

PATHOLOGY AND PATHOGENESIS

Freiman and Hardy studied the histopathology in lung specimens for 130 cases of chronic beryllium disease from the Beryllium Case Registry (5). Six cases were acute and 124 chronic disease. Their observations have provided a useful pathologic categorization for chronic beryllium disease and correlation between histopathologic changes and clinical course.

Their description of the changes in six patients who died of acute disease was that of non-specific acute and subacute bronchitis and pneumonitis. Interstitial and intra-alveolar edema,

alveolar cell proliferation and desquamation, cellular infiltration with lymphocytes and plasma cells, hyaline membranes, and organizing pneumonia were important features. No associations between type or severity of these changes and the known clinical manifestations could be made.

Characteristic changes of chronic beryllium disease are those of chronic interstitial pneumonitis with noncaseating granulomas. Histiocytes, lymphocytes, and plasma cells comprise the cellular infiltrates. Giant cells, asteroid bodies, and calcific inclusions in granulomas are seen frequently.

Chronic cases were divided into Groups IA, IB, and II based on granuloma formation and cellular infiltration (Table II-26). Eighty percent of cases were in Group I and 20% in Group II. Histopathology in Group II was indistinguishable from that observed in sarcoidosis and was associated with a better prognosis and a better response to steroid treatment, compared with Group I (A and B) patients. Fibrosis was present in a large proportion of cases and was variable in degree in different parts of the lung.

Noncaseating granulomas have also been found in lymph nodes, liver, skin, spleen, and other tissues. Representative histopathology from lung and mediastinal lymph nodes is shown in Figures II-38 and II-39.

In animal experiments using several different species, beryllium has been found to be toxic by all routes of administration including intravenous, inhalation and tracheal instillation, intraperitoneal, and subcutaneous instillation. Toxicity by the oral route has been found to be low. Both acute pneumonitis and chronic pulmonary granulomatous disease have been produced in experimental animals exposed to beryllium.

In humans, the disease is caused by inhaling beryllium in all forms with the exception of beryl ore, which has not caused beryllium disease.

The mechanism of action of beryllium in producing acute respiratory tract disease is most likely that of direct toxic effect on mucosal surfaces, causing edema, inflammation, and necrosis. The pathogenesis of the chronic disease is not certain, although a suggested mechanism is that beryllium combines with immunoglobulins, causing the release of toxic substances and subsequent transport of a protein-beryllium complex to extrapulmonary tissues. Beryllium is

Table II-26
HISTOLOGICAL CLASSIFICATION OF CHRONIC BERYLLIUM DISEASE

Histological Characteristics	Subgroup IA	Subgroup IB	Group II
Interstitial cellular infiltration	Moderate to marked		Slight or absent
Granuloma formation	Poorly formed or absent	Well formed	Numerous and well formed
Calcific inclusions	Variable; frequently present and numerous		Few or absent

Source: Freiman and Hardy (5)

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distributed widely in the body and has been found in many organs and tissues. Excretion is slow and by the renal route. Beryllium may be detected in urine up to 20 years after a patient's last known beryllium exposure.

Immunologic and hypersensitivity mechanisms in the pathogenesis of chronic beryllium disease have been proposed by several investigators. Deodhar et al. studied blast transformation of lymphocytes in the presence of beryllium sulfate (in tissue culture) from patients with chronic beryllium disease, exposed healthy workers, unexposed healthy controls, and patients with other lung diseases (3). Strongly positive (3 or 4+) results were found in 60% of patients with chronic beryllium disease and in only one healthy, unexposed control. The authors indicated a good correlation between severity of disease and amount of lymphocyte transformation. Preuss reported the usefulness of blast transformation of lymphocytes in separating groups of patients with chronic beryllium disease from those with sarcoidosis (18). Price et al. reported results of the beryllium macrophage migration inhibition test in 5 patients with chronic beryllium disease, 20 healthy controls, and 50 healthy beryllium workers (19). They demonstrated the production of a macrophage migration inhibition factor from lymphocytes in the 2 patients with chronic beryllium disease not receiving steroids, in 7 healthy beryllium workers presumed to be sensitized to beryllium, and in none of the controls. These studies suggest that cell-mediated immunity to beryllium is involved in the generation of tissue changes in chronic

beryllium disease. This is also compatible with observed histologic changes.

CLINICAL DESCRIPTION

Symptoms and Signs

Clinical manifestations of beryllium disease are divided into acute and chronic effects of beryllium exposure. Acute disease has been defined as those beryllium-related conditions that last for less than one year and occur during exposure to beryllium. Acute disease is dose-related and similar to acute tracheobronchitis or pneumonitis caused by the irritant gases. Chronic disease lasts longer than one year and, although patients may develop the disease during beryllium exposure, the onset of disease may follow cessation of exposure by weeks to years. The chronic disease is a pulmonary and systemic granulomatous disease for which no dose-response relationship has been established.

Acute dermatologic manifestations include dermatitis appearing one to two weeks after initial exposure to soluble salts of beryllium and associated with a positive skin patch test to soluble beryllium compounds. A hypersensitivity mechanism has been generally accepted for this disease form because of the observed latent period between exposure and onset; skin patch test reactions; and reports of subsequent dermatitis in previously sensitized individuals, appearing more rapidly and after less intensive exposure. After exposure ceases, the dermatitis resolves usually within two weeks. Immediate reactions of dermatitis may occur in previously

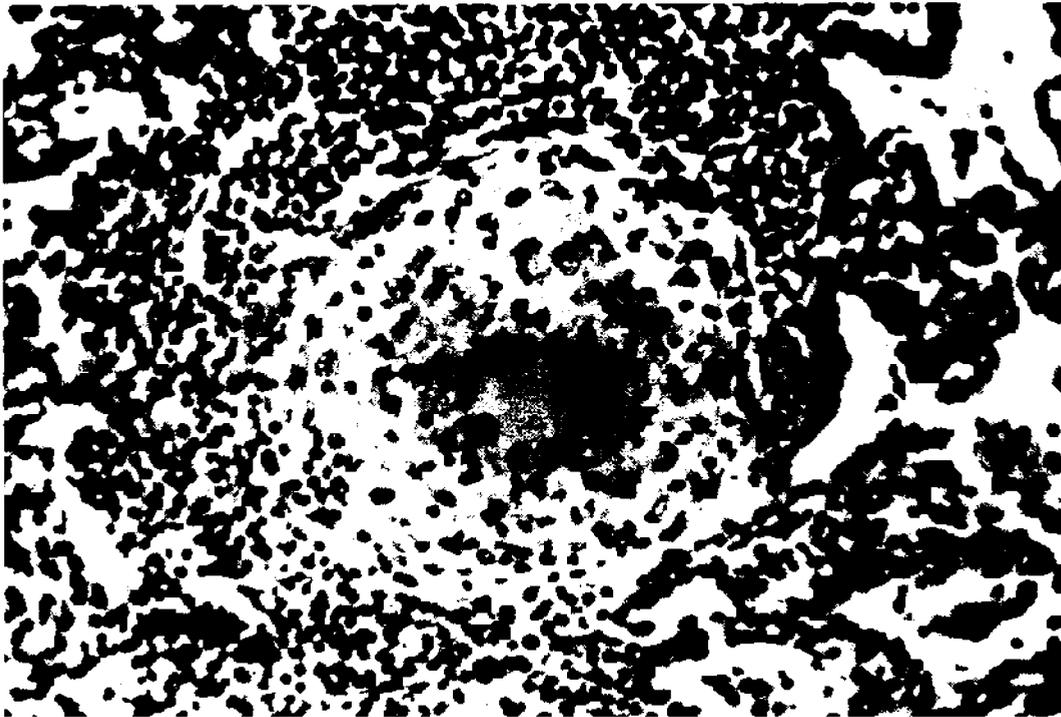


Figure II-38. Chronic beryllium disease, lung, Group IB. This biopsy specimen shows marked interstitial cellular infiltration and a well-formed granuloma containing a giant cell.

unexposed patients and are related to primary irritation, secondary to a high concentration of beryllium exposure on the skin. Conjunctivitis, periorbital edema, and upper respiratory tract involvement may accompany dermatitis.

Localized skin ulceration secondary to beryllium contamination of a wound or direct implantation of beryllium into the skin have been reported in the past. Healing usually requires removal of beryllium from the ulcer.

Acute nasopharyngitis has been associated with beryllium exposure. Symptoms include pain, swelling, bleeding of the nose and pharynx; objective signs include edema, hyperemia, and bleeding points. Fissures and ulcerations occur in untreated cases. Three to six weeks after exposure ceases, nasopharyngitis has usually resolved.

Acute tracheobronchitis secondary to beryllium exposure has been observed. Onset and course of this clinical pattern may be severe and rapid or subacute and slower, depending on the level of exposure. Symptoms are chest discomfort, nonproductive cough, and dyspnea. Physical findings include hyperemia of the upper respiratory tract and rhonchi and rales on

auscultation of the chest. Increased bronchovascular markings have been described on chest x-ray. Therapy is cessation of exposure and bedrest; recovery is usually complete within one month.

Acute chemical pneumonitis is the most serious of acute diseases related to beryllium exposure. Chemical pneumonitis secondary to beryllium exposure may be severe and fulminant after brief exposure to very high concentrations of beryllium or more subacute in onset and course after prolonged exposure to lower concentrations. Fatal cases are rare; resolution is generally complete by six months. Symptoms and signs are similar to those found with other causes of chemical pneumonitis. Symptoms are dyspnea, cough and substernal pain. Blood-tinged sputum, weight loss, and fatigue have been reported associated symptoms. Physical signs are tachypnea, tachycardia, rales, and cyanosis in severe cases. Radiographic findings are diffuse or localized infiltrates or haziness of lung fields. Laboratory findings are unremarkable. Reduced lung volumes and hypoxemia characterize acute pneumonitis. Therapy is determined by the disease's severity. Bedrest, observation for



Figure II-39. Chronic beryllium disease, mediastinal lymph node. This biopsy specimen shows some well-formed granulomas and intense cellular infiltration.

pulmonary edema, and supplemental oxygen and corticosteroids (if indicated) are recommended therapy modes.

Acute beryllium disease is currently rare. In the last six years, only one case of acute beryllium disease has been reported to the Beryllium Case Registry. Out of 892 cases of beryllium disease on file with the Beryllium Case Registry, 212 represent acute disease. According to Registry data, approximately 17% of patients with acute disease have developed chronic disease. Factors accounting for the occurrence of chronic disease in individuals who have had previous acute disease are unknown at present.

Chronic beryllium disease is the pulmonary and systemic granulomatous disease caused by beryllium exposure. The duration of exposure in reported cases is generally several months to years. The latent period between initial exposure and onset of disease is variable but averages 10 to 15 years. Disease may occur while a patient is still exposed to beryllium or may follow cessation of exposure by up to 25 years.

The severity of disease varies from an asymptomatic patient with only radiographic

abnormalities to severely disabled patients with chronic respiratory failure and cor pulmonale. The lungs are almost invariably affected. A report by Stoeckle et al. of 60 patients with chronic beryllium disease indicated that 95% had dyspnea, the most frequent symptom (25). A recent review of BCR data by Hasan and Kazemi indicated in 76 cases, exertional dyspnea was the most common presenting symptom followed in frequency by cough, fatigue, weight loss, and chest pain (10). Unusual initial symptoms were arthralgias, fever, orthopnea, anorexia, hemoptysis, palpitations, convulsions, wheezing, nausea, vomiting, and hoarseness.

Results of physical examination vary. Abnormalities include bibasilar rales; accentuation of the pulmonic component of the second heart sound if pulmonary hypertension is present; peripheral lymphadenopathy, skin lesions, hepatosplenomegaly, and clubbing. Signs of cor pulmonale may occur in long-standing, advanced cases. Parotid gland enlargement has been reported in one patient with chronic beryllium disease (10). The physical examination may also be entirely normal in chronic beryllium disease.

Clinical Course

The collected experience of clinicians following patients listed with the Beryllium Case Registry has been that chronic beryllium disease follows a variable clinical course. Some patients have a stable course for many years followed by eventual deterioration. Patients with radiographic abnormalities and no symptoms may have a stable course or develop symptoms after a variable time. There are reports of numbers of patients who have improved without treatment. One case of complete resolution of symptoms, signs, and nodules on chest x-ray, temporally related to adrenocorticotrophin (ACTH) therapy, has been reported by Stoeckle et al. (25). Although results of controlled trials are not available, it is the impression of clinicians who have followed large numbers of patients with chronic beryllium disease that corticosteroid therapy improves symptoms, signs, clinical course, and radiographic abnormalities in many treated cases. Early improvements in lung function (including lung volumes and alveolar-arterial oxygen tension differences ($A-aD_{O_2}$) at rest) have been reported by Gaensler et al. in patients treated with corticosteroids, although improvement was not sustained (6). There is an indication that the pattern of lung function abnormality may affect the clinical course. A study by Andrews et al. of lung function in 41 patients with chronic beryllium disease revealed three patterns of abnormalities: restrictive, obstructive, and interstitial defects (1). The last group comprised 36% of the cases and was characterized by reduced carbon monoxide diffusing capacity, widened $A-aD_{O_2}$ at rest, and exercise hypoxemia. That group had the least deterioration of function five years later compared with the obstructive and restrictive groups. Almost all patients in the groups were receiving chronic corticosteroid therapy.

A recent longitudinal study of beryllium production and extraction workers at one plant suggested that medical surveillance programs of currently exposed workers may be used to detect beryllium disease at an early stage and that the disease may be reversible when beryllium air concentrations are lowered (12)(21). The initial observations of those workers showed that 14% had interstitial abnormalities on chest x-ray, 9% had hypoxemia, and 5% had both hypoxemia and interstitial infiltrates at a time when peak beryllium air concentrations were elevated above

the peak acceptable level of 25 mg/m^3 in 60% of samples taken. Three years later, after peak air concentrations were all lowered to less than 25 mg/m^3 , workers had improvements in hypoxemia and resolution of interstitial infiltrates even though none had received therapy, stopped smoking, or changed jobs. Six years after the initial survey, peak air concentrations of beryllium were still lower and further radiographic resolutions were noted by Sprince et al. (20).

Laboratory Investigations

Pulmonary Function Tests

Early reports of lung function changes in chronic beryllium disease emphasized a restrictive defect characterized by reduction in lung volumes, normal airflow rates, hypoxemia at rest (exacerbated by exercise), and reduced diffusing capacity for carbon monoxide. More recent data from the Beryllium Case Registry reported by Andrews et al. showed that of 41 patients with chronic beryllium disease, only 20% had a restrictive defect, while 39% had an obstructive pattern, 36% an interstitial defect, and 5% were normal (1). Table II-27 summarizes lung function abnormalities associated with the three groups. The obstructive pattern, which occurs in both smokers and nonsmokers, is associated with peribronchial location of granulomas. Prognosis was best for the interstitial group, which showed very little deterioration at five-year mean follow-up; it was worse for the obstructive and restrictive groups, both of which showed worsening of physiologic impairment in spite of continued corticosteroid therapy. Cor pulmonale was frequent in the obstructive group. A recent study by Kanarek et al. suggests that mild interstitial disease, secondary to beryllium exposure, may only be characterized by mild hypoxemia and mild increase in $A-aD_{O_2}$. (12).

Radiologic Studies

Typical radiographic features in chronic beryllium disease are diffuse infiltrates and bilateral hilar lymphadenopathy (see Figure II-40). These abnormalities are not diagnostic for chronic beryllium disease and similar changes occur in sarcoidosis, silicosis, and some cases of tuberculosis. The radiographic densities have been classified as granular (which measure up to 1 mm in diameter), nodular (1 mm to 5 mm in diameter), and linear. Mixed patterns of den-

Table II-27
CRITERIA FOR CLASSIFYING LUNG FUNCTION TESTS
IN CHRONIC BERYLLIUM DISEASE

Type of Defect	Lung Function Criteria for Group
Interstitial	<ol style="list-style-type: none"> 1. Normal ventilation and lung volumes 2. Carbon monoxide diffusing capacity less than 80% of predicted
Restrictive	<ol style="list-style-type: none"> 1. Vital capacity less than 80% of predicted 2. Normal Forced Expiratory Volume in 1 second (FEV₁) 3. Total lung capacity (TLC) less than 80% predicted
Obstructive	<p>Three of the following:</p> <ol style="list-style-type: none"> 1. FEV₁ less than 72% 2. Peak expiratory flow rate less than 80% of predicted 3. Maximum breathing capacity (MBC) less than 80% of predicted 4. Residual volume/total lung capacity (RV/TLC ratio) greater than 30% 5. Helium equilibration time greater than 2.5 min.

Source: Andrews, Kazemi, and Hardy (1).

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sities may occur, and densities may increase, diminish, or remain stable. In a recent Beryllium Case Registry review of 69 patients' radiographic patterns by Hasan and Kazemi, a mixed pattern with granular, nodular, and linear densities was observed most frequently (36%). This was followed by a mixed pattern with fibrosis in 30%, a nodular pattern in 14%, and granular densities in 6% (10). Among those patients, 35% had hilar lymphadenopathy, and in 83% of those, the enlargement was bilateral. Hilar enlargement has been described in 45% of another series of 60 Beryllium Case Registry patients reported by Stoeckle et al. (25). Hilar adenopathy alone, without parenchymal lesions, is rarely the presenting feature of chronic beryllium disease. The radiographs of one patient with this uncommon presentation who went on to develop interstitial infiltrates are shown in Figures II-41 and II-42. Calcification of pulmonary densities and hilar lymph nodes has been reported by Stoeckle et al. (25). Pleural thickening, cysts, a single nodule, and pneumothorax have been reported but are uncommon. Contraction of upper lobes with hyperinflation of lower lobes has been found in long standing cases.

Other Laboratory Abnormalities

Hypergammaglobulinemia (mainly IgG or IgA), elevated erythrocyte sedimentation rate, and erythrocytosis may be seen in patients with chronic beryllium disease. Hyperuricemia, hypercalciuria, and hypercalcemia are associated laboratory abnormalities in some patients.

Associated Abnormalities

Chronic beryllium disease is associated with extrapulmonary abnormalities in most cases.

This histopathology is usually noncaseating granulomas with the finding of elevated beryllium content in these extrapulmonary tissues. Thoracic and other lymph nodes may be involved and a report by Hasan and Kazemi has shown markedly elevated beryllium content in chronic beryllium disease in mediastinal lymph nodes (10).

Skin involvement associated with chronic beryllium disease (and not as a result of contact dermatitis or direct implantation of beryllium on the skin) is that of nodular lesions showing non-caseating granulomas when biopsied. Hepatosplenomegaly has been observed in 11% of patients and noncaseating granulomas have been found on liver biopsy.



Figure II-40. Chest radiograph showing typical features of chronic beryllium disease, namely diffuse interstitial densities and bilateral hilar lymphadenopathy.

Renal calculi have been reported in 3% to 7% of patients with chronic beryllium disease. Hypercalcemia has been observed in 1% to 4% of patients and hypercalciuria in 1% to 20%. The mechanisms for renal stone formation and abnormalities in calcium metabolism are unknown at present.

Hyperuricemia, probably secondary to impaired renal clearance of uric acid, was reported by Kelley et al. in 6 of 15 patients with chronic beryllium disease (14).

Rare manifestations of chronic beryllium disease include parotid gland enlargement, central nervous system granulomas and restrictive cardiomyopathy reported by Sprince et al. (24).

Treatment

The only available therapy for chronic beryllium disease is corticosteroids. In some cases, clinical impressions are that therapy may alter the course of the disease favorably, although no long-term cures have been reported. Lifetime therapy with an oral corticosteroid is usually required and exacerbations of symptoms and radiographic abnormalities have been reported after withdrawal of corticosteroids.

As in other chronic pulmonary diseases, supplemental oxygen therapy may improve hypoxemia and should be considered in patients who develop significant hypoxemia. Therapeutic modalities which may be useful for complicating right heart failure and pulmonary hypertension include supplemental oxygen for severe hypoxemia, diuretics, and possibly digitalis. Prevention of serious bacterial and viral infections is also important. To that end, antibiotic therapy for suspected acute bacterial tracheobronchitis and immunizations to prevent influenzal and pneumoconial infections should be employed.

Prognosis

The variable clinical course has been outlined in a previous section. To date, 41% of the 892 patients listed with the Beryllium Case Registry are known to be deceased.

DIAGNOSTIC CRITERIA

The diagnosis of beryllium disease is based on consistent radiographic, physiologic, and histopathologic features in a patient with documented significant exposure to beryllium. Investigators working with the Beryllium Case Registry have established six criteria for the

Table II-28
CRITERIA FOR THE DIAGNOSIS OF BERYLLIUM DISEASE

1. Establishment of significant beryllium exposure based on sound epidemiologic history
2. Objective evidence of lower respiratory tract disease and a clinical course consistent with beryllium disease
3. Chest x-ray films with radiologic evidence of interstitial fibronodular disease
4. Evidence of restrictive or obstructive defect or diminished carbon monoxide diffusing capacity
5. Pathologic changes consistent with beryllium disease on examination of lung tissue and/or thoracic lymph nodes
6. Presence of beryllium in lung tissue or thoracic lymph nodes or other tissues or the presence of beryllium in a urine specimen

Source: Kazemi (13)

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diagnosis of chronic beryllium disease, based on collected information from hundreds of cases of the disease since the Registry was established in 1952. These criteria are presented in Table II-28. To make the diagnosis of chronic beryllium disease, 4 to 5 criteria must be presented. To confirm significant exposure to beryllium, all cases must include either criteria 1 or 6.

Establishing an exposure history may be difficult. Frequently, exposures occurred many years prior to a patient's medical attention. Inadequate labeling at the time of exposure and memory problems compound the difficulty. Objective information confirming exposure may be obtained by finding beryllium in biopsy specimens (usually lung and thoracic lymph nodes) or in urine. Beryllium is excreted slowly and may be found in urine up to 20 years after the last exposure to beryllium. These findings help confirm exposure only and not the presence or absence of disease related to exposure.

Criteria 2 to 5 (Table II-28) are self explanatory and have been discussed under clinical description.

Investigators working with the Beryllium Case Registry have found that tissue analysis for beryllium in lung and thoracic lymph nodes is a useful method to document beryllium exposure and to differentiate chronic beryllium disease from sarcoidosis. Using the modified Morin fluorometric method of analyzing for beryllium (reported by Walkley (29)), Sprince et al. showed

that levels greater than 0.02 μg beryllium per gram dried tissue are found in 82% of the lung specimens of chronic beryllium disease cases (24). In normals and in patients with sarcoidosis, beryllium levels are all below 0.02 μg per gram dried tissue. Elevated mediastinal lymph node beryllium content has been reported by Hasan and Kazemi and is helpful in establishing a diagnosis (10). The combination of an elevated content of beryllium in tissue with compatible histopathologic changes confirms the diagnosis of chronic beryllium disease in many cases. If exposure is well documented and the non-invasive clinical criteria (criteria 2-4, Table II-28) are met, diagnosis may be made without the necessity of a biopsy of the lung or mediastinal lymph node.

Some investigators with experience in tests of cellular immunity have found other tests—namely blast transformation of lymphocytes, and tests of beryllium macrophage migration inhibition—useful in the diagnosis of chronic beryllium disease and would include these tests in the diagnostic criteria.

Mention should be made of the beryllium patch test—a skin test for documenting hypersensitivity to beryllium—reported by Curtis. This test probably has no current clinical usefulness in diagnosis because of false negatives, induction of sensitivities of previously unexposed individuals to beryllium, and the possibility of exacerbating respiratory tract involvement by application of the skin test.

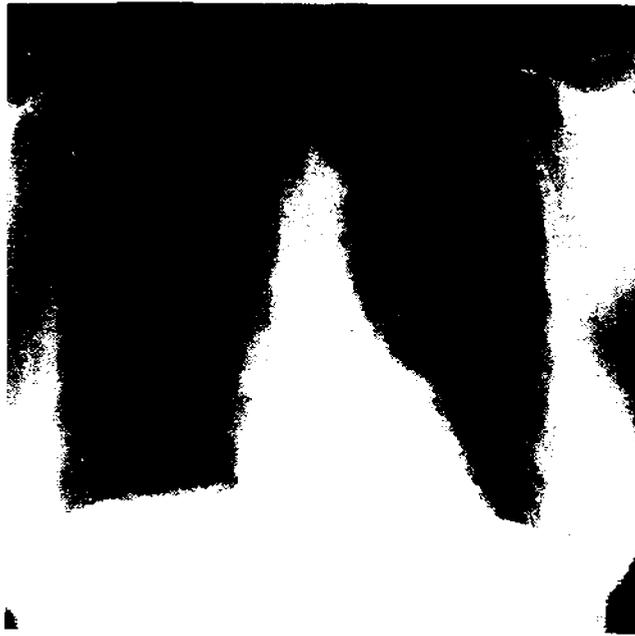


Figure II-41. Chest radiograph showing a rare presentation of chronic beryllium disease, isolated bilateral hilar lymphadenopathy. The patient is a 48-year-old woman who presented with no symptoms and with a normal physical examination. She had worked from 1940 to 1946 manufacturing fluorescent lamps. Mediastinal lymph node biopsy revealed noncaseating granulomas and an elevated beryllium content of 0.32 μg per gram dried tissue.

DIFFERENTIAL DIAGNOSIS

The diagnosis of chronic beryllium disease is frequently difficult. Other diseases which enter into differential consideration include idiopathic pulmonary fibrosis, miliary tuberculosis, fungal diseases, pulmonary hemosiderosis, lymphangitic carcinoma, hypersensitivity pneumonitis, silicosis, and other pneumoconioses. The most difficult differential is between chronic beryllium disease and sarcoidosis because these diseases share similar signs, symptoms, radiographic abnormalities, lung function findings, and histopathology.

Useful differential features between chronic beryllium disease and sarcoidosis have been recently reviewed by Sprince et al. (24). To date, uveitis, uveoparotid fever, cranial and peripheral nerve involvement, and cystic bone lesions have been reported in sarcoidosis but not in chronic beryllium disease. Complete resolution of radiographic abnormalities (common in sar-

coidosis) is rare in chronic beryllium disease. The Kveim test (tissue levels of beryllium and serum angiotensin—1 converting enzyme (ACE) levels) may aid in differentiating these diseases. The Kveim test, which is positive in approximately 80% of sarcoidosis patients, has been negative in all chronic beryllium disease patients tested. Lung tissue from patients with chronic beryllium disease contains higher concentrations of beryllium than lung tissue from controls and patients with sarcoidosis. If elevated, serum ACE levels are more suggestive of sarcoidosis than chronic beryllium disease, since 48% of sarcoidosis patients have elevated ACE levels, compared with only 1 elevated level in 22 patients with chronic beryllium disease tested in a recent report by Sprince et al. (21). However, Lieberman et al. have reported elevated ACE levels in 3 of 4 patients with beryllium disease who were tested (15). Data from larger numbers of patients are needed before the usefulness of ACE levels in differential diagnosis is established.



Figure II-42. Chest radiograph from same patient presented in Figure II-41, taken three years after the initial film and showing bilateral hilar lymphadenopathy with the new finding of mild interstitial infiltrates.

PREVENTION

Control of beryllium air concentrations is the major mode of beryllium disease prevention. In the 1940's, large numbers of patients with beryllium disease were reported; their exposures occurred mainly in atomic research, beryllium extraction, and fluorescent lamp manufacturing. In 1949, the Atomic Energy Commission adopted limits for beryllium exposure in the workplace of $2 \mu\text{g}/\text{m}^3$, averaged over an 8-hour day, and $25 \mu\text{g}/\text{m}^3$ as the peak limit value at any one time during the day. By 1950, beryllium was discontinued from use in fluorescent lamp manufacturing and endeavors to control air concentrations of beryllium were instituted in extraction and other operations.

Reports from the Beryllium Case Registry indicate that, after 1950—probably because of reduction of beryllium air concentrations in industry—numbers of reported cases of acute and chronic beryllium disease decreased significantly.

Although standards for beryllium exposure

have existed since 1949, industries where beryllium levels exceed acceptable standards have been reported in the 1970's. Technology is available to control beryllium in air and to meet currently accepted standards. Since control measures may be associated with prevention or reversal of disease, they should be instituted widely in all beryllium-producing or utilizing operations.

It has been an overall clinical impression that chronic beryllium disease does not develop in workers whose exposure to beryllium has been in compliance with the current standards. However, after viewing all available information, including data on carcinogenic effects of beryllium, OSHA has recommended a reduction to $1 \mu\text{g}/\text{m}^3$ as an 8-hour time-weighted-average with a $5 \mu\text{g}/\text{m}^3$ ceiling value and no peak allowable standard.

The usefulness of detecting the individual worker who may develop beryllium disease on the basis of tests of delayed hypersensitivity has

no established role in prevention of disease to date.

As for acute disease, there is general agreement that controlling elevated air concentrations of beryllium has been effective in preventing its occurrence.

RESEARCH NEEDS

Scientific investigations have covered many aspects of beryllium disease, since the initial reports of the disease in the United States by Van Ordstrand et al. (28) and Hardy and Tabershaw (9). Many questions have been answered so that at this time beryllium disease has decreased in importance as a public health problem.

One remaining question which has not been satisfactorily answered to date, is that of the mechanism of disease production. The relative roles of dose-response relationships and immunologic or individual factors in the chronic disease need clarification and further longitudinal studies of workers exposed to beryllium would be useful to answer this question.

As stated previously, the discrepancies in estimates of the population at risk require further clarification.

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PULMONARY REACTIONS TO MISCELLANEOUS MINERAL DUSTS, MAN-MADE MINERAL FIBERS, AND MISCELLANEOUS PNEUMOCONIOSES

Stuart M. Brooks

INTRODUCTION

The miscellaneous pneumoconioses represent a group of occupational lung disorders caused by the inhalation of a variety of different dusts. The entity does not include the dusts of silica, asbestos, silicates, coal and carbon products, various clays, beryllium, or organic dusts. Most miscellaneous pneumoconioses are due to inorganic materials, mainly metals of one sort or another. In reviewing the miscellaneous pneumoconioses, the definition provided by Parkes has been adapted: "The presence of inhaled dust in the lungs and their nonneoplastic tissue reaction to it."

A large number of different occupations, industrial processes, and materials must be considered. As a group, the miscellaneous pneumoconioses can potentially affect an estimated working population of ten million. While the total number of exposed workers at risk may be large, the actual number of individuals employed in any single industry or exposed to any specific agent may not be large when compared to inorganic dusts such as asbestos, coal, or silica. Only aluminum and iron, with perhaps several million potentially exposed workers, approach the population exposure magnitude of these other dusts.

A problem in identifying affected individuals may be related to the fact that only a small number of workers are usually employed in any single operation/industry and thus exposed to one of the dusts. Consequently, medical and environmental information is not as readily available as it is in larger industries where occupational health programs are better developed, regulated, and supervised. Another consideration is that many of the miscellaneous pneumoconioses cause only chest radiographic alterations but are not associated with medical dis-

ability or symptomatology. Because of this, there is less interest or impetus to monitor these workers. On the other hand, the agents to be described in this chapter have extremely important, often critical, uses and demands in this country, as well as throughout the world. The demand for these agents will be generally increased over the next 10 years, consequently increasing the number of workers exposed to them. It is important to be familiar with the miscellaneous pneumoconioses and to make practicing physicians more aware of their presence, of their manifestations, and of the occupations where these lung diseases are likely to occur.

ALUMINUM

Introduction

The primary sources of aluminum are the ores of cryolite and bauxite; the metal is never found in its elemental state (Al). Aluminum's effect on the lungs differs depending upon the composition of the inhaled aluminum-containing dust. Cases of pulmonary fibrosis sometimes called "Aluminum Lung" (25), as well as asthma have been reported in workers involved in various manufacturing processes.

List of Causative Agents (Manufacturing Processes)

The estimated annual capacity of primary aluminum production is 14 million tons (27). There are three major steps in aluminum production beginning with mining of the ore (bauxite) and leading to production of metal ingots. Bauxite mining consists of strip mining or underground mining depending upon the type of vein to be quarried. Bauxite contains alumina which is mixed with 40% to 50% iron and other oxides. Extraction of alumina (aluminum oxide, Al_2O_3) from the ore involves preferentially

dissolving it out by autoclave treatment with soda (Bayer Process). Filtration of the caustic mixture leaves a residue known as red mud and a solution of pure alumina in soda. Alumina is then precipitated from the soda by means of a seeding process. The solution is allowed to settle, then filtered and calcined from drygin to yield the alumina—a white, floury powder (27). The final step is carried out either in smelters or reduction plants. The basic reduction process involves an electrolytic decomposition: alumina is first transformed into a liquid form in order to allow a direct electric current to pass through it. Because alumina has such a high melting point (close to 2,000 °C), operations at such temperatures are impractical, if not impossible. To get around this problem, a fluorinated compound of sodium and aluminum (cryolite) is used. It melts at approximately 1,000 °C and in a molten state is capable of dissolving up to about 8% of alumina (27). Thus, alumina is obtained in a liquid form by dissolving it in molten cryolite at a temperature below 1,000 °C where it is technically more practical and feasible to carry out electrolysis. The molten aluminum produced by electrolysis has a slightly higher specific gravity than molten cryolite and therefore will settle into the bottom of the cell from whence it can periodically be extracted by some kind of vacuum trapping technique. The electrolytic process is done in an electrolytic cell (called the pot) which consists of steel-coated shells lined with insulating materials and contains an electricity-conductive bottom made of carbon connected to a negative polarity power source. Carbon anodes connected to positive polarity hang above and dip into the cryolite-alumina melt. When electric current flows from the anode to the cathode bottom, alumina is split into metallic aluminum spreading over the bottom and evolving oxygen. The capacity of a common pot is approximately 150,000 amps and yields more than one metric ton of aluminum each day (27).

There are various pot-fume emissions that have been identified (27). Molten cryolite releases gaseous hydrofluoric acid and fluoride dust. Fluoride emissions are low during quiet operations but increase during crust breaking, taping, and anode-changing (27). In addition to the generation of cryolite dust, there is also production of alumina and carbon dusts, the proportions depending upon the raw materials used. During the burning of the anodes, sulfur diox-

ide is emitted, having originated from the sulfur present in the petroleum coke used for anode making. Anode burning involves oxygen during electrolysis and results in the evolution of carbon monoxide and carbon dioxide gases.

Depending on the type of pot used, there are also emissions of various pitch volatiles and polynuclear aromatic compounds. Identifying specific etiologic agents causing lung disease among reduction workers is difficult because they may be exposed not only to alumina but also to a number of other air contaminants including: asbestos, which is sometimes used as insulation in the pots or as marinite in casting operations; carbon, used to make cathodes and anodes; fluorides, emitted both as a particulate and gas which are constituents of cryolite and of the electrolytic bath; and particulate polycyclic organic matter, originating from the binder used in the electrodes (40). Secondary chemical contaminants that are present include: carbon monoxide, a by-product of incomplete combustion which can be present at low levels in pot-rooms having inadequate ventilation; copper fumes and dust which occur from some anode rods and fluxes as well as from welding and sanding; cyanide, which may be emitted in spent cathode material but is usually not a problem unless acidified; mercury, contained in electrical rectifiers which may be present during maintenance work; perchlorethylene, used as a solvent degreaser on electrical parts and motors; silica, sometimes used in sandblasting and also found in discarded refractory bricks; and sulfur dioxide, a by-product of sulfur-bearing coke. Various welding fumes may also be present in the working environment: chlorine gas may originate from fluxing and casting operations; hydrogen chloride can be formed during casting from chlorine and water; manganese fumes can occur during processing metal alloys; ozone can be produced as a by-product in electrical discharge and welding; and phosgene can result from combustion products of halides (39).

There are two major types of aluminum products produced—flakes and granules. Particle size as small as 0.6 μ have been noted in the flaked type, which are prepared in a stamp or ball-mill from cold metal or foil (25); the granular type is made from molten metal (25). Stearin, a mixture of fatty acids created by hydrolysis of fats or paraffin, is usually added to allow separation of particles (24). Many of

the early cases of pulmonary fibrosis attributed to aluminum exposure were reported in Germany during World War II when stearin was not added to the flakes (25). Furthermore, there are reports of pulmonary fibrosis among English and Swedish stamping mill workers, where stearin was either reduced or replaced by mineral oil (25).

Small-sized, flaked particles (pyro) are used in the manufacture of explosives and incendiary devices and fireworks. Some occupations in which exposures may occur to the flaked variety include: aluminum alloy grinders, reduction plant workers, ammunition makers, fireworks makers, foundry workers, petroleum refinery workers, plastic workers, and rubber makers.

Hazardous exposures may occur during smelting and refining processes. Aluminum may be alloyed with copper, zinc, silicone, magnesium, manganese, or nickel (34). Special additives may include chromium, lead, bismuth, titanium, zirconium, and vanadium (34). Aluminum and its alloys can be extruded or processed in rolling mills, fireworks, forges, or foundries and are used in ship building, electrical building, aircraft, automobile, light engineering, and jewelry industries. Aluminum foil is widely used in packaging.

Powder aluminum is used in pyrotechnic industries (34). Alumina has been utilized as abrasives, refractories, catalysts, and in the past, in the first firing of china and pottery (34). Aluminum chloride is used in petroleum processing and in the rubber industries. Heavy aluminum compounds are used as catalysts in the production of polyethylene.

Bauxite, a noncrystalline mineral, has a composition of $Al_2O_3 \cdot 2H_2O$ and theoretically contains 74% alumina (usually closer to 50-60%). It is the major aluminum ore, but is also used in the manufacture of abrasive aluminum salts, refractories, white cement, and as a replacement for fuller's earth for decolorizing oil (2). Bauxite contains varying amounts of silica (2-10%), iron oxide (2-26%), and titanium oxide (2-4%) (2). Aluminate cement is a construction cement containing bauxite as a raw material. It has quick-setting properties, reaching a strength in 24 hours as high as that obtained by ordinary cement in 28 days; thus it is useful in laying roads or bank walls. American bauxite found in Arkansas, Georgia and Alabama is valued for aluminum production because of its

low silica content (2).

Alumina, the natural crystalline form of aluminum (Al_2O_3) is used as an abrasive and for gem stones (2). It is an important constituent of clay, used for making porcelain, bricks, pottery, and refractories. It may also be used as a mordant in dyeing. Hydrated alumina is used as catalyst carrier and has particles which are 0.1 μ to 0.6 μ in size. It can also be used as a filler in plastics and cosmetics. Calcined alumina is alumina that has been calcined to a degree that prevents absorption of more than 0.5% to 2% water. It is a fine powder and is used for electrical insulators, abrasives, and in porcelain and ceramic enamel mixes. Aluminum hydrate is a white, bulky water-insoluble aluminum powder ($Al(OH)_3$) produced by the reaction of soluble aluminum salt and alkali and precipitated from a solution (2). It is used as a base for lake pigment, for making glass white, as a water repellent agent, and for fabric and paper coatings. Hydrated alumina coated with stearic acid is used as a reinforcing pigment for rubber.

Aluminum is a bluish-white metal with countless uses. It is used for automotive and airplane construction, for moving parts of machinery, for ornamental or architectural work, and for cooking utensils. The metal is transparent to x-ray and is used in thin sheets as a ray filter. Its lightness makes it valuable for transport equipment; about 25% of its entire production is used for this purpose. It is resistant to corrosion and is nonmagnetic even when alloyed with iron (2). Aluminum sheets as thin as 0.0005 inch are rolled into aluminum foil. Aluminum, in powder form, is used in paints and fireworks. Its physical properties are greatly affected by even slight additions of other elements. So great is the effect of alloy elements in aluminum that a commercial aluminum 99.2% pure will have a strength 25% greater than 99.9% pure aluminum. Pure aluminum is next to gold in malleability. Aluminum alloys are usually aluminum-copper alloys with or without other alloying elements. Copper hardens and strengthens aluminum. The alloy is easy to cast; 8% copper is considered the economic point for balancing strength and low specific gravity. When zinc and tin are added to aluminum alloys, they cause hot-shortness; silicon adds fluidity and decreases luster; magnesium inhibits grain growth and gives age hardening; titanium gives corrosion resistance; and iron in small amounts increases

strength. Nickel, replacing copper in the alloy, makes it stronger, more corrosive resistant and improves luster (2).

Aluminum oxide (Al_2O_3) may be made commercially and, because of its high melting point, is valuable as a refractory material. The crystalline type is used as an abrasive. Aluminum oxide is also employed in making refractory linings and crucibles. Aluminum oxide grains can be made into pellets with a ceramic bond for use as a catalyst carrier in the chemical industry. Alumina, the natural-occurring crystalline aluminum oxide is called corundum; the synthetic crystals used for abrasives are designed as aluminum oxide or marketed under trade names. It is an important constituent of clays for making porcelain, bricks, pottery, pigments, catalyst carriers, chemicals, and refractories—although aluminum metal production and abrasives are its major uses. Ultrafine aluminum abrasive powders are of two types: alpha-alumina with hexagonal crystals and gamma-alumina with cubic crystals. The alpha type cuts faster but the gamma type gives a finer finish. The aluminum oxide most frequently used for refractories is beta-alumina with hexagonal crystals heat-stabilized with sodium.

The Hindu word, corundum, was originally applied to gemstones (2). Rubies and sapphires are corundum crystals colored with oxides. Oriental topaz is yellow corundum containing ferric oxide. Oriental emerald is a rare green corundum. Corundum is now largely replaced by the more uniformly manufactured aluminum oxide. Foamed aluminum or aluminum foil is made by foaming aluminum metal with zirconium hydride or other metal hydride (2). Released hydrogen expands the metal into cellular structures of good strength and controlled densities which can be used for insulating roofing or for building panels.

Aluminum powder or flake, made by a stamping process, is used as a pigment in paints and printing inks, in silvering rubber articles, and in plastics. Spherical-shaped particles of aluminum free from grease (granulated aluminum) are used in coloring and for pyrotechniques and explosives, fat reacting fuels, and incendiaries. Aluminum powder may be used to increase thrust in solid-fuel rockets, for metallurgical purposes, for paints and enamels.

Aluminum-silicon alloys refers to casting alloys containing 5-22% silicon. They are char-

acterized by their ease of casting, corrosion resistance, lightness, and ease of welding. They are frequently used for engine cylinders, pistons, and casting dies. Aluminumized steel consists of dip-coating and diffusing aluminum into steel at a temperature of about 1,600 °F to form an aluminum-iron-alloy coating. The process is used for wire, sheet, and marine hardware.

List of Occupations and Industries Involved

Exposure to aluminum as a powdered metal occurs in a number of occupations where aluminum is used or processed:

- Aluminum workers
- Aluminum smelting
- Aluminum alloy grinders
- Ammunition makers
- Fireworks maker
- Aluminum paint makers
- Aluminum propeller grinders
- Petroleum refining
- Plastic makers
- Rubber makers

Exposure to aluminum oxide is seen in:

- Abrasive manufacturers
- Pot-room workers
- Catalyst makers
- Aluminum grinders
- Potteries
- Refractories

Epidemiology

Shaver and Ridell described a lung disease in Canadian pot-room workers exposed to fumes which evolved during the making of abrasive corundum (naturally occurring Al_2O_3 in alpha or hexagonal crystals, usually containing lime and other impurities) (29)(30). During the operation, dense white fumes were noted to evolve and tended to be carried upward by the heat draft from the furnaces, with most of the fumes escaping through openings in the roofs of the furnace rooms. Nonetheless, considerable contamination occurred in the work area surrounding the furnaces where workers were stationed (29)(30). A total of 23 cases of pulmonary fibrosis were described—ages ranging between 25 and 61 years and length of exposure 29 months to 15 years. The majority of affected employees worked as “furnace feeders.” An additional 25 workers were studied and 13 showed “early” or “doubtful” pulmonary fibrosis. Symptoms varied in intensity but were found to correspond to the

amount of lung involvement present as indicated by a chest x-ray (30).

Shaver commented on the high concentrations of alumina and silica in a finely divided state evolving from the reduction process. The atmosphere contained 32.3% silicon dioxide and 56% aluminum oxide. The silica, however, was present in an amorphous nonfibrogenic form (14). Particles were extremely small, 0.02 to 0.5 μ in diameter. The disease was fatal in seven cases, and in several other cases progressed rapidly, producing serious disability. Of 245 individuals exposed in four different plants, 35 had "definite" x-ray changes of disease, and 13 had lung changes classified as "doubtful." The etiology of the fibrosis was uncertain.

Pulmonary fibrosis was noted in workers exposed to very fine aluminum powder used for fireworks and aluminum paints (20). The powder was produced by pounding cold metal into fine flakes used for fireworks (pyro) and paint powders (20). Exposure to high concentrations of dust occurs when machines are emptied and filled and during certain weighing and screening processes (29). Goralewski reported that German workers engaged in the manufacturing of pyro-aluminum powder not coated with stearin developed acute respiratory illnesses within a few months of starting work (10). The development of illness was rapid and showed no relationship to length of exposure to aluminum.

Hunter reported on airplane propeller grinders in England during the war (14). Duraluminum is an alloy containing 95% aluminum, 3.5-4.5% copper, 0.04-0.7% iron, and 0.3% titanium. It was used for making aircraft propellers, and during this process propellers were ground smooth with alundum wheels (calcined aluminum oxides 95-97%, ferric oxide 0.3-0.6%, titanium oxide 2.2-2.8%, and silica 0.2-0.4%) which created much dust. Despite good ventilation, workers were covered with dust and were said to assume an aluminum color. The average concentration of aluminum in the breathing zone of operators was 3-5 mg/m³. At polishing vents, dust levels were on the order of 50-100 mg/m³, depending on the direction of the buffing wheel. The dust was almost exclusively large aluminum particles, although a significant number of particles below 2 μ were present. Clinical examinations revealed no excess illness recorded in medical records, nor were there abnormal chest x-rays noted in 92 workers examined.

Mitchell reported a fatal case of progressive pulmonary fibrosis in a young man occupationally exposed to high concentrations of fine aluminum dust (23). On postmortem examination there was a generalized pulmonary fibrosis present, most marked in the upper lobes. Many jagged particles were identified in lung tissue and gave histochemical reactions for aluminum. The average content of aluminum oxide per dry weight of lung was 640 ppm (23). While the particle size of the powder was generally large, dust levels of about 10 mg/m³ consisted of dust particles less than 5 μ . The dust was mixed with approximately 0.5% stearin.

Mitchell et al. reported on 27 individuals in a fireworks factory exposed to pyro (finely powdered aluminum); six workers had evidence of pulmonary fibrosis (24). This study involved exposures to fine, flaked aluminum powder which is made by stamping cold metal. Whereas flaked powder is flattened and has a peculiar leafing characteristic, granulated powder consists of larger particles which are spherical in shape and is widely used in aluminum paints. Large quantities of stearin were used for paint powder to prevent aggregation of particles, but the making of pyro powders required the quantities of stearin to be kept as low as possible and replaced largely by mineral oil. Exposure to high concentrations of dust took place while aging and emptying machines during certain weighing and screening processes. Mean total dust concentration in the pyro stamping room during emptying and refilling of machines was 6.5 mg/m³ and 68 mg/m³ (24); respirable dust was 51 and 52 mg/m³ (respirable dust was 8% of the total dust). There was a mean concentration of 95 mg/m³ of respirable dust in the screening room. Chemical analysis of dust revealed that aluminum represented 81.4% and stearin approximately 3.5%. Semiquantitative spectrographic analysis showed 0.5% silicon dioxide and approximately 0.1% copper manganese and iron to be present; beryllium was not detected.

One of the first cases of pulmonary fibrosis was reported in German aluminum workers by Baader in 1934 (24). After World War II, cases of pulmonary fibrosis were reported in men working with aluminum powder for ammunition (24). Goralewski reported on 62% of the workers from six factories and noted more than 26% had pulmonary fibrosis (9). Koelsch, summarizing German workmen's compensation cases, re-

ported 65 cases in which 26 were considered cases of "aluminum lung" (19). In Japan, Ueda recorded a case of a patient who died of an aluminum-associated lung disease three years after stopping employment (36).

Jordan reported pulmonary fibrosis in a young woman employed for five years as a "flash filler" in a fireworks factory and exposed to high concentrations of aluminum powder (17). Pulmonary function studies showed reduced lung volumes and severely impaired carbon monoxide diffusion (17).

Clinical, radiographic, pathologic, and environmental features of a case of extensive pulmonary fibrosis were reported in a 49-year-old man who worked 13½ years in a ball-mill room of an aluminum powder factory and died with progressive encephalopathy and seizures (21). There were no presenting pulmonary symptoms. Chest x-ray examinations of 53 other workers in the same factory and pulmonary function studies of 23 individuals revealed no significant abnormalities. The concentration of aluminum in lung and brain tissue was about 20 times normal and in the liver, 122 times more than in the normal controls. Microscopic studies of lung tissue revealed aluminum particles in areas of fibrosis. Chemical analysis confirmed the presence of aluminum in the lung. Sections of brain tissue also indicated aluminum deposition in brain tissue.

Posner and Kennedy reported on china biscuit placers, more than half of whom were working with aluminum for more than 15 years. No cases of radiologically manifest pulmonary fibrosis were identified (26).

Discher and Breitenstein reported a prevalence of chronic pulmonary disease in 457 male aluminum pot-room workers compared to a 5.3% prevalence rate in 228 skilled laborers (7). No difference was noted in respiratory symptoms or spirometric measurements between the two groups. Jephcott reported that the bauxite used by the plants reported by Shaver contained between 77.5% and 85.2% Al_2O_3 and 4.5-7.2% SiO_2 (16). Chemical analysis of fumes indicated concentrations of $SiO_2 \cdot O_2$ of 30.7-62.1%. Analysis of lung tissue from the autopsy of six workmen exposed to the fumes showed silica concentrations of 0.86-2.45% per dried lung and alumina content of 1.2-2.6%. The amount of alumina and silica were in excess of the quantities observed in lungs of unexposed persons and indicated

that significant amounts of inhaled fumes were retained by the lungs. X-ray defraction analysis of dried lung revealed both alpha and gamma alumina.

Estimates of Population Exposed

The National Occupational Hazard Survey (NOHS) conducted by NIOSH estimates that there may be more than three million workers potentially exposed to various aluminum compounds. About 1.8 million are exposed directly to alumina (Al_2O_3)—perhaps 112,000 on a full-time basis. It is estimated that 1.6 million are exposed to aluminum coated with stearin—25,000 on a full-time basis, and that 500,000 are directly exposed to aluminum metal (35).

Pathology

Autopsy studies on gross examination have shown the lungs are usually either small or normal in size and weight, but sometimes markedly shrunken (28). Pleural surfaces are pigmented and may have a somewhat pebbled appearance. On occasion, there may be extensive thickening of the pleura, with emphysematous blebs and large bullae present on the surfaces. The darkly pigmented fibrous masses and bands are scattered throughout lung substance tissues on cut sections of the lung. Central portions of the lung between the pleural surface and hilum are most heavily involved, demonstrating areas of dense fibrosis (28). Fibrous extensions cross interlobular septums to the pleura and appear to pass inward toward the hilum along the bronchi and blood vessels. The bronchi appear to be of normal appearance grossly, but may be dilated, containing clots of coagulated exudates. Moderate thickening of the vessels is noted. Lymph nodes are pigmented and firm, but may be slightly enlarged.

Microscopic examination discloses diffuse nonnodular fibrosis of the lung. The fibrous tissue is said to be hyaline in nature with a few areas of interstitial inflammation. Alveolar spaces may be partially occluded and compressed between bands of collagen. Some airspaces contain masses of phagocytes filled with blackish pigment, giant cells containing cholesterol crystal clefts, and cellular debris. The alveolar walls are thickened and lined with cuboidal epithelium. Dilated bronchi containing mucus may be seen in some areas; the submucosa is often thickened

and shows inflammatory cell reaction. Vessels, while usually normal, may show perivascular fibrosis and occasionally endarteritis. Lymphoid tissue reveals evidence of lymphadenitis, with large numbers of phagocytes filled with pigment particles within lymph nodes (28)(40).

One mechanism, which could explain the fibrogenic effects of aluminum on lung tissue, proposed that in the presence of protein and chloride ions, the protein is tanned and is then co-precipitated with an aluminum hydroxide complex which covers the partly dissolved aluminum particles (15). This complex is relatively insoluble and not likely to be phagocytized (3)(4)(15). Koelsch believed that the reported lung disease was the result of poor workroom ventilation present in blackouts during World War II, and that this led to high concentrations of aluminum dust accumulating in the ambient air of the work environment (19). The observation that excessively high workplace concentrations of aluminum dust are important in disease production is supported by studies of Gross et al. (11), who investigated pulmonary reaction to three types of aluminum powder: 1) British pyro powder, composed of flake-like particles; 2) American-made flake-like powders; and 3) American atomized spherical particles. Pulmonary fibrosis did not develop in guinea pigs and hamsters following inhalation of large dust burdens. Intratracheal injection of large doses of aluminum powder, however, did cause focal fibrosis. This was believed to represent an artifact due to the method of administration and the high concentration of dust used (11). Instillation of lower concentrations of aluminum dust, for instance, did not cause fibrosis.

Pulmonary fibrosis has not been reported in workers exposed to granular type alumina dust (Al_2O_3), such as when working in stamp mills that produce aluminum powder for paint and ink manufacturing (5); in aluminum reduction plants (18)(22); in potteries (26); or among Duralumin airplane propeller polishers (14). A proposed mechanism to explain the lung damage suggests that the introduction of mineral oil into the stamping industry, in place of stearin, permitted the powder to react with water, whereas it did not before. Lung damage was, therefore, caused by contact with the soluble aluminum. When pulmonary fibrosis has been reported, the incriminated dust has usually been flaked aluminum in which mineral oil was used to coat the

flakes, either partially or wholly replacing stearin (9)(24). (There is an exception, however, in a case reported by McLaughlin et al. (22).) Thus aluminum oxide covering granular powder particles and stearin covering flake particles, was thought to prevent metallic aluminum from exerting a fibrogenic effect (11). Animal studies, however, do not support this theory since intratracheal instillation of fine aluminum flakes coated with either stearin or mineral oil were fat-free (3), but caused fibrosis of equal severity. Granular aluminum powder, however, had a negligible effect and was essentially inert (3).

It has also been suggested that silica, present in cryolite, was a responsible factor (1). This seems unlikely since quartz probably would be converted to glass at the operating temperature of the furnaces and identification of tridymite or cristobalite in the fumes had not been reported (25). Metallic aluminum, when heated in fumes, evolves mainly gamma-type Al_2O_3 (8), which causes fibrosis in rat lung, whereas alpha-type Al_2O_3 does not (32). Styles et al. tested alumina in cell cultures and in animals to assess its cytotoxicity and tissue reaction (33). The toxicity of alumina to rat peritoneal macrophages in cell culture was low when compared to asbestos. However, alumina fibers caused more fibrosis than zirconia fibers when injected intraperitoneally in animals (33). Although an immunologic reaction in aluminum workers with lung fibrosis has been described there is no conclusive evidence to support this hypothesis.

Thus, the role of aluminum dust or fumes in the pathogenesis of lung fibrosis is uncertain. The variability of animal study results makes it difficult to correlate with human disease. Even so, there are a number of reports of workers who have been exposed to both dust and fumes, and who have developed pulmonary fibrosis without identifying any other causal factor for their lung disease. It can be concluded, therefore, that aluminum may sometimes be responsible for causing pulmonary fibrosis, but the exact occupational circumstances and conditions are not yet completely clear.

Clinical Description

The pulmonary fibrosis attributed to aluminum is associated with two different inhalable materials (25): fumes derived from the smelting of bauxite (Al_2O_3), (known as Shaver's disease after Shaver jointly described the association in

1947 (30); and inhalation of aluminum dust (25).

Shaver described unilateral or bilateral spontaneous pneumothoraces (30). Chest x-rays, when reviewed, showed well-established pulmonary fibrosis. Dyspnea on exertion was an outstanding symptom with attacks of extreme breathlessness frequently described. Attacks of breathlessness were occasionally interspersed with periods of symptom improvement. The majority of workers gave a history of cough and sputum production. The sputum was described as white, fluffy, or frothy in character, sometimes mucopurulent. In addition, there were complaints of substernal chest discomfort or tightness and occasionally actual chest pain. Weakness, fatigue, and inability to sleep were seen in individuals with severe dyspnea. No specific abnormal physical findings were noted in individuals with early disease, but in those with advanced disease, weight loss and loss of appetite were apparent. Chest signs, when present, were variable and largely depended on the presence or absence of pneumothorax and the amount of pulmonary fibrosis. More advanced cases showed cyanosis and limited chest expansion. Furthermore, decreased percussion noted on physical examination was generally found to correspond with extensive pulmonary fibrosis or pleural thickening. In some instances there was elevation of the diaphragm. Hyperresonance and decreased breath sounds were associated with the presence of pneumothorax. Some individuals demonstrated friction rubs; rales, and rhonchi were noted on chest auscultation (30).

In most cases chest x-ray showed widening of mediastinal shadows and irregular borders of the diaphragm shadow. The diaphragm was often tented and markedly elevated. Interstitial changes noted on chest x-ray were more pronounced in the upper lung fields, more intense towards the hilum, and less toward the periphery. Coarse shadows throughout the lung field occurred in more advanced cases. Emphysematous changes were often present and associated with bleb formation (30).

In workers exposed to fine aluminum powder, there were complaints of dry cough, pleuritic-like chest pain, shortness of breath, poor appetite, and gnawing abdominal pain (13) (24). Spontaneous pneumothorax occurred in some workers. Eosinophilia as high as 10% in

some workers was present; erythrocyte sedimentation rate was normal in the majority of workers. A restrictive lung defect was noted on pulmonary function studies with decreased vital capacity. X-rays showed pulmonary fibrosis affecting mainly the upper part of the lung. Increased markings in the upper and middle thirds of the lung fields provided a reticular appearance, which later increased to become confluent. In general, symptoms and signs were similar to those in Shaver's disease.

There have also been a number of reports of an asthma-like syndrome associated with working in the pot-room environment (18)(31) (37)(38). Clinically there is an immediate asthmatic response while workers are actively working in the pot-rooms, usually precipitated by high exposures to pot fumes. A second, delayed response occurs 4 to 12 hours after leaving the cell room; a third, or dual-type, occurs in individuals both at work and sometimes after work (6). The asthmatic syndrome seems to occur following exposures to both pot-room fumes and dust (38). The immediate type of response usually develops within three months of employment; delayed responses usually occur after three months or as late as three years following beginning employment (6). Those with dual responses usually develop asthma within 6-12 months. Asthma occurs equally in both atopic and nonatopic individuals. The syndrome may appear after only one pot-room exposure. A major complaint is a nonproductive cough. Dyspnea is a more prominent symptom in individuals with immediate-type responses, whereas wheezing is prominent in workers with the delayed-type response. Those with the dual-type syndrome have severe exertional dyspnea (6). The exact cause of the asthma from pot-room exposure has not been identified.

Diagnostic Criteria

The most difficult problem is to distinguish this disease from mixed dust fibrosis and sometimes asbestosis. Differentiation is possible only when an appropriate and complete occupational history is taken and all exposures are identified. There are no specific diagnostic features of the history, physical exam, pulmonary function tests, or chest x-ray which differentiate this disease from other forms of pulmonary fibrosis.

Methods of Prevention

There are a number of fume control devices. Pots are generally fitted with a primary collection system and may also have a secondary system (27). The fumes collected by the primary collection system are concentrated and can be treated using either an electrostatic filter or bag filter, or a dry scrubbing system (27). A secondary system does not exist in every smelter but usually consists of a water scrubbing system on the roofs of the building, abating the pollutants that may have escaped during the primary system.

Research Needs

The exact mechanisms to explain the pulmonary fibrosis described in aluminum workers needs to be elucidated. It is not clear whether aluminum alone, or in combinations with other materials, is capable of inciting a fibrotic response. The specific etiological agents responsible for asthma among pot-room workers need identification.

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ANTIMONY

Introduction

Antimony is an extremely brittle metal, bluish-white in color and crystalline-like in texture. Like arsenic and bismuth, it is sometimes referred to as a metalloid; it should be called a semimetal. It does not have the free cloud-like electrons that occur in metal atoms, thus it lacks

plasticity and is a poor conductor of electricity. It is used only in alloys or in chemical compounds. It is easily reduced to powder and is neither malleable nor ductile (2).

List of Causative Agents (Manufacturing Processes)

The chief uses of antimony are in alloys, especially as a hardener for lead-base alloys (2). It imparts hardness and a smooth surface to soft-metal alloys because it expands on cooling. Alloys containing antimony are useful because they can reproduce the fine detail of a mold, thus making it valuable for type metals. When alloyed with lead, tin, and copper it forms *habbitt* metals that can be used for machinery bearings. Antimony compounds are also widely used for pigments, particularly as a paint pigment for coloring red rubber and in safety matches.

The chief antimony ore is stibnite (Sb_2S_3). Other antimony ores are valentinite, an oxide with a rhomboid structure; cervantite or antimony tetraoxide (Sb_2S_5O); stibiconite ($Sb_2O_4 \cdot H_2O$); kermesite (Sb_2S_3O), a mineral resulting from the partial oxidation of stibnite; Jamesonite ($Pb_2Sb_2S_5$), another sulfide ore of antimony; and stephanite, ore of silver sulfantimonite ($AgSbS_4$). Antimony is obtained chiefly as a by-product or co-product of base material and silver ores and is used in a variety of industries (27). Most industrial exposures are to antimony dusts rather than to antimony fumes, with antimony trioxide dust being the most common.

Antimony is used in electronic semiconductors and thermoelectric devices because of its excellent specific heat and electrical resistance (26) (27). The light transmitting qualities of antimony compounds, particularly antimony trioxide, make them ideal pigments for ceramics, glass, metalware, and enamels. Plastic flame-retardant chemicals are also important products (25).

U.S. consumption of primary antimony was slightly more than 15,000 short tons (21). Antimony is alloyed with other metals such as tin, lead, and copper. Metallurgical processes utilizing antimony compounds include the use of lead-antimony for the manufacture of storage battery grinds, pewter, type metal, printers' type, lead shot, lead electrodes and bearing metals, collapsible tubes and foil, sheet pipe, solder, cable covering, and castings. Antimony compounds are used in the rubber industry especially in the com-

pounding of rubber. Antimony trioxide is used in flame-proofing materials for application to textiles and as a flame retardant in paint pigment. Oxides are used as opacifiers in enamels and as a decoloring and refining agent in glass manufacture. Other uses include bronzing powder for metals and plaster, ammunition primers, and fireworks (4)(21)(27). NIOSH estimates that there are approximately 50 potentially hazardous antimony compounds (12).

About 25 countries throughout the world are involved in antimony production (27). In 1976, the United States imported roughly 24,000 tons of antimony metal oxide and ore for consumption (21). U.S. production totaled approximately 35,000 tons, of which approximately 42% came from primary sources such as ore and primary smelters and 58% was secondary or recycled metal (21). Secondary antimony is recovered chiefly from battery scraps.

List of Occupations and Industries Involved

Table II-29 lists occupations and industry in which exposure to antimony may occur (12).

Epidemiology

Renes reported pneumonitis, tracheitis, laryngitis, and bronchitis among workers exposed to antimony trioxide (22). Karjovic demonstrated x-ray evidence of pneumoconiosis in 14 of 62 workers in an antimony smelting operation exposed to concentrations of poorly defined mixed dust (ranging from 16-248 mg/m^3). The dust contained antimony oxides and some silica. While the antimony oxides represented the bulk of the dust, it was not clear what role silica had (10). Exposure to antimony trioxide and other metal dusts produced x-ray changes in 44 of 262 workers (17). Workers with abnormal chest x-rays were essentially asymptomatic. Microscopic examination of tissue from one worker who died showed an accumulation of dust particles and dust-laden alveolar macrophages within alveolar septa and perivascular tissue. There was no evidence of pulmonary fibrosis or interstitial inflammatory response (15)(16). Cooper et al. reported three definite and five suspicious cases of pneumoconiosis based on chest x-ray changes in a group of 28 workers exposed to antimony ore and antimony trioxide (4). LeGall reported reticulonodular x-ray changes in 10 of 40 workers exposed to a mixed dust (including silica) containing an-

Table II-29

OCCUPATIONS WITH POTENTIAL EXPOSURE TO ANTIMONY

Antimony ore smelters	Metal bronzers
Antimony workers	Miners
Babbitt metal workers	Monotypers
Battery workers, storage	Mordanters
Brass founders	Organic chemical synthesizers
Britannia metal workers	Paint makers
Bronzers	Painters
Burnishers	Perfume makers
Cable splicers	Pewter workers
Ceramic makers	Pharmaceutical workers
Compositors	Phosphor makers
Copper refiners	Pigment makers
Dye makers	Plaster cast bronzers
Electroplaters	Porcelain workers
Explosive makers	Pottery workers
Fireworkers makers	Printers
Flame retardant workers	Pyrotechnics workers
Foundry workers	Rubber makers
Glass makers	Semiconductor workers
Glaze dippers, pottery	Solder makers
Gold refiners	Stereotypers
Insecticide makers	Stibnite miners
Insulators, wire	Textile dryers
Lake color makers	Textile flame-retardant workers
Lead burners	Textile printers
Lead hardeners	Type metal workers
Lead shot workers	Typesetters
Linotypers	Vulcanizers
Match makers	Zinc refiners

timony metal and trioxide (13). Some workers reported symptoms of shortness of breath, cough, and sputum production and demonstrated some abnormal physical findings. The role of silica and of SO₂ in the production of the lung changes and symptoms was not clear (13). One affected worker, however, worked only at the antimony oxide furnace where antimony exposure was reported to be high and silica concentrations low or nonexistent.

Estimate of Population at Risk and Prevalence of Disease

NIOSH estimates that 1.4 million U.S. workers are potentially exposed to antimony in their occupational environment (25). Exposures are largely to metal alloys and to metal oxide and sulfides.

Pathology

Histological examination of antimony workers' lungs reveal only dust accumulation and no fibrosis (16). Alveolar macrophages containing dust particles congregate in alveolar walls and around small vessels (16). No fibrosis or significant inflammatory reactions have been reported (16).

While antimony ore or antimony trioxide have not been reported to cause significant fibrosis in experimental animals (4), there have been reports of pulmonary reactions to certain antimony compounds in man following exposure by several routes (10)(13)(15)(17)(22)(24). A pneumonitis occurs following inhalation of antimony trioxide in guinea pigs (6). Animals with more than 50 mg of antimony in their lungs

showed scattered subpleural hemorrhages (6). Lipoid pneumonia was noted to occur in rats following inhalation of antimony trioxide for 25 hours per week over 14.5 months (8). Pathologically, there was evidence of cellular proliferation and swelling and desquamation of alveolar lining cells. Subsequent studies reported more deaths due to pneumonia among the exposed animals and evidence of extensive interstitial pneumonia and some fibrosis. The initial pathologic response was an acute chemical pneumonitis (4). By two months, only alveolar accumulation of macrophages was noted. No fibrosis was noted in animals followed as long as one year after termination of exposure. Single instillations of 2.5-20 mg of antimony trifluoride intratracheally in rats are invariably fatal (14) and result in acute hemorrhagic pulmonary edema. Tracheal instillation of antimony trisulfide or pentasulfide results only in macrophage accumulation, slight perivascular and peribronchial cellular inflammatory reactions, and scattered areas of atelectasis (14).

Clinical Description

There are no specific clinical symptoms or abnormal physical findings in workers exposed to antimony compounds (19). Health problems from antimony include dermatitis, mucous membrane irritation, electrocardiographic alterations, liver involvement, and hematologic changes (2)(3)(4)(5)(7)(10)(11)(13)(15)(17)(18)(22)(23). Many of the symptoms ascribed to antimony may be due to arsenic which is a common contaminate of antimony ores and antimony compounds used in industry.

Pulmonary Function Studies

There are no abnormalities of lung function reported.

Radiographic

There have been occasional reports of chest x-ray changes. Usually this consists of small, dense opacities similar to those noted in siderosis or stannosis (4)(15)(17). Large, confluent shadows do not occur. Densities may be denser near the hilar regions with loss of well-defined hilar vascular shadows (19). X-ray changes can develop within two to three years and involve all portions of the lung. Opacities are regular, usually 1-3 mm in size (9)(20). There are no detrimental effects upon health or life expectancy. Unlike siderosis and barium inhalation, there is no

evidence of decrease in the x-ray appearance with progression of time following cessation of exposure (19).

Diagnostic Criteria

Antimony pneumoconiosis is a rare condition which can be overlooked if an accurate occupational history is not obtained. Differential diagnosis is similar to that for other inert dusts which are of high radio densities, such as tin or barium (which may produce identical x-ray appearances). Miliary tuberculosis can be easily excluded because of its clinical presentation; its opacities also are reported to be less dense and well-defined and may be more profuse in the mid zones of the lung (19). Sarcoid may present with a nodular pattern but is usually associated with large hilar adenopathy and other characteristic features of this disorder. Opacities seen with pulmonary hemosiderosis are due to repeated capillary hemorrhage and should be easily differentiated by hemoptysis, anemia, clubbing, and hepatosplenomegaly.

Methods of Prevention

NIOSH has recommended concentrations of antimony in the workplace should not exceed 0.5 mg/m³ as determined by a time-weighted-average concentration for up to a 10-hour workshift in a 40-hour week. A workplace medical program should include both preplacement and periodic examinations including chest x-rays and pulmonary function studies (25).

Proper protective clothing may be necessary and should include gloves, coveralls, head and neck protection, and also eye and face protection if necessary. Respiratory protection is only indicated when engineering controls have not yet taken place; in situations where installation and testing of engineering controls are occurring; during performance of certain maintenance or repair procedures; and during emergencies where high dust levels may be expected.

Research Needs

More epidemiologic studies are needed to better define the prevalence of disease if it does occur. Animal studies might be designed to better identify which of the antimony salts is more likely to be toxic.

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BARIUM

Introduction

Barium is a silver-white metallic element found in the widely distributed minerals witherite and barite. Although barium can be obtained by electrolysis from barium chloride, it oxidizes so readily it is difficult to process in the pure metallic state. Because of this, barium compounds find the most extensive uses.

Baritosis, first described by Arrigoni among barytes miners in Italy (1)(2), results from the inhalation of respirable particles of barium sulfate causing dense radiologic opacities but no functional impairment.

List of Causative Agents (Manufacturing Processes)

Barium may be extracted from barium oxide by heating with aluminum in vacuo at about 1,200 °C and then condensing the barium vapor in the cool end of a tube. It may also be extracted with ferrosilicon at a temperature about 50 °C higher. Lead barium-calcium alloys are prepared by electrolysis of the chlorides in cells with molten lead at the cathode (3).

Barium sulfate is insoluble and is used as a radiopaque contrast media for radiologic studies. It is not absorbed by the gut. On the other hand, soluble salts of barium are generally toxic. For example, barium carbonate, barium chloride, barium nitrite, and barium sulfide are rapidly absorbed by the gastrointestinal tract and are fatal to man in amounts of less than one gram (6). This type of intoxication is not often recognized clinically; it is usually noted only at postmortem examinations.

Barytes are widely distributed through the world and occur in combination with other minerals such as fluorite, calcite, limestone, witherite, quartz, and chert which may be intermixed according to the type of deposits (10). Barytes from some areas contain significant

amounts of free silica. In the United States, the major states producing barytes are Nevada, Missouri, Arkansas and Georgia.

List of Occupations and Industries Involved

Barium compounds are used in the manufacture of lithopone (a white pigment utilized in paints), chlorine, sodium hydroxide, valves, and green flares (14). Barium compounds are used in synthetic rubber vulcanization, x-ray diagnostic work, glass making, paper making, meat-sugar purification, and animal and vegetable refining (14). Compounds are also used in the manufacturing of brick and tile, pyrotechnics, and in the electronics industries. In addition, they are used as additives to lubricants, pesticides, glazes, textile dyes and finishes, pharmaceuticals, and in cements which will be exposed to salt water. Barium is used as a rodenticide; as a flux for magnesium alloys; as a stabilizer and mold lubricant in the rubber and plastics industry; as an extender in paints; as a loader for paper, soap, rubber, and linoleum; and as a fire extinguisher for uranium and plutonium fires. It is used as an extender or filler in cement, paint, paper, soap, rubber, linoleum, plastics, ceramics, electronics, and in the glass industry, and in compounds containing matches, and in art paint pigments.

A list of jobs where exposure to barium compounds may occur includes: textile workers, chemical workers, tile makers, lithopone manufacturers, fire extinguisher makers, oil workers, pesticide(s) manufacturers, x-ray diagnostic contrast material workers, and barium miners (baryte ore).

During mining of the crude baryte ore, high concentrations of dust are produced, which may include silica in cases where the surrounding rock contains silica in hydrothermic deposits or chert. Baryte is supplied to industries in crude form, after removal of contaminants (10). Chances of dust inhalation during this procedure are low because operations are usually accomplished in the wet state. During drying and bagging of ground barytes, high concentrations of dust may be produced (10).

Ground baryte is used in the oil industry as a wetting agent for drilling mud; as a filler with weight increasing properties in some types of paper; as an additive in linoleum, textile, rubber, brake linings, and enamel paints; and in glass industries to increase the fluidity of molten glass

(10). It was used in records until the introduction of microgroove records in about 1948. Lithopone, a widely used pigment and filler until recent years, was made by roasting crude silica-free barytes with carbon in a rotary kiln, bleaching out the product and then adding zinc sulfate. The resulting precipitate was washed, filtered, dried, and calcined. At some stages of the process, a mixture of barytes and carbon dust was present. Coal was often used as a source of carbon and grinding was a dusty process. Because of this, the possibility of coal or carbon pneumoconiosis coexisted with baritosis. Today, the production of lithopone has markedly decreased.

Barium, in the form of barytes or witherite, is used in large quantities by the chemical industry. Because of its electromagnetic properties, barium titanate has been used for electronics and ultrasonic devices including transducers and digital computers. Accidental inhalation of barium sulfate during x-ray contrast studies (such as upper GI series) sometimes occurs, but it is not likely to be confused with baritosis of industrial origin.

Epidemiology

Doig reported nine cases of baritosis occurring in a small factory in which baryte was crushed, grated, and milled (4). Two of the cases occurred after 18 and 21 months of exposure; 9 of the 10 men employed for more than 1-1/2 years had baritosis. Five of the affected men examined—who left the industry and had no further exposure—showed clearing of radiologic abnormalities.

Pendergrass reported a case of a man working in a lithopone plant who was exposed to finely divided particles of barium sulfate (11). The worker also had been a coal miner for 4 years and an engine cleaner in a railroad shop for 12 years. During his employment he was also exposed to silica and carbon dust, but mainly barium dust. Chest x-ray showed nodular-like opacities distributed throughout both lung fields. Autopsy examination of lung tissue revealed the presence of irregular masses of dense fibrous tissue scattered throughout the lung. Some of the nodules were characteristic of silicosis but shaded with heavy carbon deposits. Polarized light examination indicated refractile crystals which were probably silica. Within the alveolar lumen there were numerous macrophages, most containing

pigmented granules. Spectrographic and x-ray diffraction studies as well as chemical analysis documented the presence of barium sulfate within the lung. The case was interpreted as being that of baritosis along with anthrosilicosis.

Estimate of Population at Risk

Baritosis is a rare condition. According to NIOSH data, however, there are approximately 800,000 exposed workers.

Pathology

Barium in the soluble form is a powerful, smooth and striated muscle stimulant (6). Accidental ingestion causes vomiting, severe colic, diarrhea, possibly gastrointestinal hemorrhage, elevation of blood pressure, convulsions, and skeletal and muscle tremors. Death occurs within one to several hours depending on the amount of barium ingested and is due to either cardiac arrest or paralysis of the central nervous system.

When free silica dust exposure occurs along with baryte dusts, both baritosis and silicosis may be present. There is no evidence that the silicotic lesion is modified by the accompanying barytes (10).

In cases of pure baritosis, cut sections of lung tissue show discrete macules located close to the pleural surface and may resemble the pathologic findings seen in stannosis (10). No confluent masses, evidence of fibrosis or hilar lymph node enlargement are noted. Microscopic examination demonstrates macular lesions similar to those seen with inhalation of tin or iron with a little reticulin and no fibrosis (10). Approximately 12 hours after endotracheal instillation of barium sulfate into rats, there is a polymorphonuclear inflammatory response in lungs containing the barium suspension (7). By 24 hours, the polymorphonuclear cells show some degeneration and are reduced in numbers. The next stage reveals mononuclear cell infiltration within the areas containing the barium suspension. By 30 days, the mononuclear cells are still present within the interstitial tissue, but may have lost their cell outline and appear to become fused together; other cells have ruptured, liberating barium salt which appears as aggregated refractile masses. By 94 to 120 days, only a mild tissue reaction remains. There are only a few areas in the lung where refractile masses remain, as well as a few lymphocytes and mononuclear



Figure II-43.

cells. There may, on occasion, be evidence of early granuloma formation, but no evidence of pulmonary fibrosis. These animal studies indicate that barium sulfate is a relatively inert substance which may cause mild tissue reaction but does not produce pulmonary fibrosis.

Clinical Description

Baritosis is symptomless and causes no abnormal physical signs. There are no symptomatic toxic effects because the baryte is a relatively insoluble, chemically inert substance.

Lung Function

No abnormalities of lung function have been recorded.

X-ray Appearance

There are discrete small opacities distributed throughout all the lung fields (see Figure II-43). They may develop with only a few months of dust exposure (9). Kerley B-lines are prominent and hilar lymph nodes are opaque but not enlarged. As in a case of siderosis, a very gradual clearing of opacities due to elimination of the dust may occur after cessation of industrial exposure (8)(13).

The outstanding feature of the x-ray is the intense radiopacity of the discrete opacities which are usually profusely disseminated throughout the lung fields (4). The appearance is always of a simple pneumoconiosis with no massive shadows. However, when the opacities are very numerous, they may almost appear confluent (12). Gambos described a background of fine, reticular, micronodular-sized opacities the size of fine sand with edges thin and sharp, contrasted and well outlined (5). In some series, the intensity and profusion of the shadows varied. The size of the shadows varied between 1-4 mm; most were 3 mm or smaller; an occasional shadow reached 5 mm (4). Nodules generally were irregular in shape, some being reticular or dendritic and occasionally round. The general distribution in the lung fields was usually uniform for the upper and lower lung fields (4). In earlier cases shadows were round and small (perhaps 1-2 mm in size) and less dense. There were no abnormalities of thoracic structure; hilar nodes were not enlarged; mediastinal distortion did not occur; and there were no adhesions or evidence of pleural thickening (4).

The presence of barytes within the lung is not known to have any adverse effects upon

health or life expectancy. On the other hand, toxic effects occur with exposure to the soluble forms of barium. There is currently no threshold limit value for barium dust classified as inert or as nuisance particulates by the American Conference of Governmental Industrial Hygienists (ACGIH).

Diagnostic Criteria

An accurate occupational history is necessary in order to diagnose barium pneumoconiosis. The marked density of opacities on chest x-ray should suggest the possibility of baritosis. When exposure to dust has been slight, or if there are only a few opacities, the x-ray may be confused with other causes of dense lung opacities. Among barytes miners where silica exposure is common, x-ray changes may be due to inhalation of silica dust (10).

Baritosis is rare among workers today, found usually in older or elderly workers who have left the industry years before. Sporadic new cases may occur, especially when men who were exposed to dust for a number of years have a chest x-ray taken for the first time (10).

Methods of Prevention

This is a rare condition. Usual procedures to reduce environmental dust levels are necessary. Soluble barium compounds should be handled carefully.

Research Needs

There are only a few reported cases of lung involvement in humans. Experimental studies on animals are limited. Further research in a multitude of areas seems appropriate.

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COBALT

Introduction

Cobalt is a silver-gray, hard, brittle, magnetic metal obtained mainly as a by-product of other metals, especially copper and silver (1)(16). It is recovered from ores by smelting in blast furnaces and then precipitated out as cobalt hydroxide; this can be inhaled, resulting in an acute tracheobronchitis (1). It has not been adequately determined whether cobalt is capable of causing pulmonary fibrosis. Cases of pulmonary fibrosis in tungsten-carbide workers have been attributed to cobalt constituents.

List of Causative Agents (Manufacturing Processes)

Cobalt is recovered as a by-product from copper and silver mining. The most important primary minerals which contain cobalt are cobalite, smaltite, and linnalite (6). Cobalt is obtained when copper-cobalt ores are reduced in electric furnaces to a crude alloy which contains about 33% to 44% cobalt mixed with iron and copper (2). Digestion with hot sulfuric acid enables the copper to be removed to filtration and the ferrous sulfate to be oxidized (2). This is then precipitated with chalk and finally filtrated. Cobalt oxides are produced from the filtrate by adding sodium carbonate, leaching it with an ammonium chloride solution, and reducing it to the metal by heating in hydrogen at a temperature of 1,000°C. An electrolytic process can also be used since deposits of cobalt are harder than those of nickel (2).

List of Occupations and Industries Involved

Cobalt is used in the manufacture of alloys with chrome, nickel, aluminum, copper, beryllium, and molybdenum, especially in the electrical, automobile, and aircraft industries (2). Cobalt steels possess some of the properties of nickel and tungsten steel; its addition to steel improves cutting qualities of tools (2)(6). A major use of cobalt is in the manufacture of pigments, especially blues for coloring glass, enamel, pottery glaze, and paints (6). Cobalt alloys are found in jet engine parts; a cobalt-chromium molybdenum alloy, vitallium, is used in orthopedic surgery because of its resistance to corrosion from body fluids (6). Ferrous and non-ferrous cobalt alloys are utilized for making powerful magnets capable of lifting loads 60 times the weight of the magnet. Corrosion resistant steel containing cobalt is used for safety razor blades and surgical instruments. Cobalt is used as a binder for tungsten-carbides and similar hard cutting materials. Cobalt may be used as a catalyst for promoting the oxidation of vegetable oils in paints. Cobalt adds a hard and brilliant surface in electroplating. Radioactive cobalt has been used for treating breast cancer (2).

A list of occupations in which exposure to cobalt may occur include: Catalyst workers, ceramic workers, drug makers, electroplaters, glass colorers, nickel workers, paint dryer makers, porcelain colorers, rubber colorers, synthetic ink makers, magnet makers, and tungsten carbide

workers (16).

Epidemiology

While there have been reports of respiratory symptoms and abnormal chest x-rays among workers in the tungsten carbide industry, opinion differs as to whether it is cobalt or tungsten carbide that is the toxic agent (2). A study by Lindgren and Ohman reported a worker who died with evidence of marked pulmonary fibrosis and bronchiectasis (8). The cobalt content of the working atmosphere dust was 2.8%. Higher concentrations of titanium and solfram were present; therefore, it was not possible to determine which dust component was actually responsible for the pulmonary fibrosis. Fairhall found no ill effect except conjunctivitis and upper respiratory irritation in workers exposed to cobalt dust (3). Miller and Davis reported three cases where chest x-rays showed increased perivascular and peribronchial markings and attributed this to cobalt (9). One case improved after removal from exposure (9). There is anecdotal data of similar cases showing clearing of chest x-rays within 18 months (9). These cases are probably due to hypersensitivity reactions. Only a few workers were affected and pure metallic cobalt did not produce similar changes.

Estimate of Population at Risk and Prevalence of Disease

It has been estimated by NIOSH that there are approximately 260,000 workers exposed to cobalt materials (19).

Pathology

Although cobalt is essential for animals' nutrition, it is probably not essential to plants (11). It is found in trace amounts in all plants except those growing on cobalt deficient soil (10)(11). Anemia develops in animals fed a cobalt-free diet; it is reversed by adding cobalt (2). Cobalt is important in the synthesis of vitamin B₁₂ (12)(15)(18).

Acute pulmonary edema and hemorrhage occur after inhalation of metallic cobalt or intratracheal instillation of soluble salts in animals (2). Harding and Delahant found that cobalt metal dust was the most toxic component of the various mixtures of substances used in the tungsten-carbide industry (5). Repeated inhalations of a mixture of 75% tungsten carbide and 25% cobalt produced pulmonary lesions while tung-

sten carbide alone and other components of the mixtures did not. Schepers reported a bronchiolitis obliterans following intratracheal cobalt metal instillation. Cobalt oxide exposed animals developed interstitial pneumonitis and diffuse granulomatous pneumonia (13). Fibrosis of alveolar septa occurred along with bronchial and bronchiolar epithelial cell hyperplasia, bronchiolization of alveolar epithelium, marked metaplastic changes, and focal emphysema and/or atelectasis. Inhaled dust was phagocytized by alveolar macrophages. The degree of pulmonary changes in cobalt oxide exposed animals generally was a function of the cumulative exposure time and was not significantly affected by cigarette smoke. There was almost complete clearing by one year (14).

In order to explain the lower toxicity of cobalt oxide compared to cobalt metal, it was suggested that cobalt oxide is converted to hydroxyl groups in body fluid, whereas cobalt metal releases cobalt ions (14). It has also been suggested that the toxic effects of cobalt are related to interference with oxidative metabolism with fixation and loss of sulfhydryl compounds in tissue (4). Cysteine, interestingly, has a detoxifying effect on cobalt (4).

Kerfoot reported animal inhalation studies in miniature swines exposed to cobalt metal powder (7). Pulmonary function testing demonstrated a decrease in lung compliance while electron microscopy showed increased septal collagen accumulation. Wehner exposed hamsters to cobalt oxide and produced acute pulmonary changes (20). The concomitant addition of cigarette smoke significantly increased the incidence of tumors but not pneumoconiotic lesions. Histological sections showed chronic-inflammatory cell infiltration of the alveolar walls and focal accumulations of cobalt oxide adjacent to bronchial and vessel walls.

Clinical Description

While there have been reports of respiratory symptoms and abnormal chest x-rays among employees in the tungsten carbide industry, opinion on the actual incrimination of cobalt as the essential toxic agent is conflicting (2). Acute conjunctival irritation and cough from respiratory irritation may occur after exposure (3). An asthma syndrome has also been described (16).

Signs

There are no specific findings.

X-rays

In general, there is no specific x-ray anomaly reported for workers exposed to cobalt except perhaps the changes described as increased vascular or bronchial lung markings (9).

Diagnostic Criteria

There are no specific diagnostic criteria identifying cobalt exposed workers other than a complete occupational history.

Prevention

NIOSH has recommended a threshold limit value of cobalt of 0.05 mg/m³ (17).

Research Needs

The role of immunologic factors in disease causation needs to be studied further. The role of cobalt in the pathogenesis of lung disease in tungsten carbide workers needs to be better defined.

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SIDEROSIS

Introduction

Iron is a malleable silver-gray metal found throughout the world, but it does not occur in its native state except in meteorites. Inhalation of metallic iron or iron compounds causes siderosis, a condition first described by Zenker in 1866 (1). Siderosis is a relatively benign pneumoconiosis, characterized by large accumulations of inorganic iron containing macrophages in the lungs with minimal reactive fibrosis. In its pure form, the condition probably does not progress to true nodulation as seen with silicosis and is usually asymptomatic. Siderosis is known chiefly for the abnormal changes produced on chest x-rays.

When iron is inhaled in conjunction with other fibrogenic mineral dusts, pulmonary fibrosis results. This is referred to as mixed dust pneumoconiosis or silicosiderosis (22). The entity known as hematite pneumoconiosis occurs in iron miners who are exposed to iron oxide in combination with free silica and silicates.

List of Causative Agents (Manufacturing Processes)

Iron is the most common commercial metal utilized in industry today. It melts at 1,525°C and boils at 2,400°C. Very small additions of carbon reduce the melting point. All commercially used irons, except ingot iron and electrolytic iron, contain some quantities of carbon which affect its properties. Iron containing more than 0.15% carbon is termed steel. Iron hardens when cooled suddenly from a red heat and when pure is very ductile. The addition of small amounts of sulfur (as little as 0.03%) causes it to become "hot-short" or brittle when red hot (3). As little as 0.25% phosphorous makes iron "cold-short" or brittle when cold. Iron is capable of forming carbonates, chloride, oxides, sulfides, and other compounds. It oxidizes easily under atmospheric conditions and is reactive to many acids. Reduced iron has special chemical uses and is made by reducing iron oxide by heating it in a stream of hydrogen.

Iron ores are iron-bearing minerals from which iron can be extracted on a commercial scale (3). Chief iron ores in order of importance are hematite, magnetite, limonite, and siderite.

The greatest producers are the United States, France, Russia, Great Britain, Brazil, and Germany. More than 90% of the iron ore mined in the United States is red hematite (Fe_2O_3) which theoretically contains 70% iron but usually not over 60%. Ores containing more than 50% iron are considered high grade. Pulverized hematite is used as a paint pigment, "Indian Red." Magnetite or magnetic iron ore ($\text{FeO}\cdot\text{Fe}_2\text{O}_3$) is found in northern New York, New Jersey, and Pennsylvania and theoretically contains 62.4% iron; it also contains some nickel or titanium. A natural magnet known as lodestone is a magnetite.

Siderite, the chief ore in Great Britain, is an iron carbonate (FeCO_3) theoretically containing 48.2% iron, but perhaps more likely 35% iron. Limonite, or brown hematite ($2\text{Fe}_2\text{O}_3\cdot 3\text{H}_2\text{O}$) is formed by the water solution of other iron minerals, and theoretically contains 59.8% of iron but usually 30% to 55%.

Emery is a naturally occurring rock which contains approximately 50% aluminum oxide (corundum), 30% hematite or magnetite, and a remainder of complex aluminum salts (2). It is frequently used as an abrasive, although synthetic materials are now also used. Emery was used by ancient Egyptians for hollowing stone vessels and cutting stone blocks and has been used since classical times for polishing marble. A pneumoconiosis has been described in metal polishers using emery (2).

Silverware is polished with "rouge" or "crocus," both of which contain iron oxide powder. The powder is applied either by hand or by a mechanical polishing wheel called a "dolly." A type of siderotic lung disease found among silver polishers has also been described (20).

Ocher has important coloring properties and qualities with such varied industrial applications as manufacture of varnish, lacquer, and linoleum. Ocherous material consists of sand mixed with clay and ferrous oxide, the latter giving ocher its yellow color. The clay consists of iron silicates or a mixture of silicates of aluminum potash or soda. The percentage of pure silica in clay is variable, but typical ocher contains about 17% iron oxide, 51% silica, and 23% aluminum oxide. Individuals who work with ocher or handle ocherous materials are thus exposed to dust which is composed mainly of silica and iron (25).

Industries and Occupations Involved

Occupational exposures to iron occur during mining, transporting, and preparing of ores; during the production and refining of metals and alloys; or while using certain iron-containing minerals. Exposure to dust of metallic iron and iron oxide may occur in a number of industries and processes (23). Metal strips in iron and steel rolling mills are agitated causing the production of rust and iron-scaled dust.

Steel grinding generates metallic dust. Welding processes utilizing electric arc and oxyacetylene torches produce iron oxide fumes (7)(13). The fume concentration may be very high for welders working in confined and poorly ventilated spaces such as tanks, boilers, and hulls of ships. Polishing of silver and steel often requires using iron oxide powder in a finely divided state, usually a specifically pure form of ferric oxide referred to as "rouge" or "crocus" (1). Ferric oxide is also used to polish plate glass, stone, and cutlery. Occupations such as fetting, chipping, and pressing castings in iron foundries are particularly risky jobs for developing x-ray changes. Siderosis may occur alone, but many times iron is mixed with silica causing a mixed-dust fibrosis or typical silicosis. Boiler scalers clean fire boxes of flues and water tubes in enclosed spaces in boilers of ships, factories, and power stations. High concentrations of dust may be generated which contain iron and perhaps carbon in coal-fired but not oil-fired boilers. Silicate and small quantities of quartz may also be present from the coal utilization; while siderosis alone may be produced, mixed-dust fibrosis also occurs. Mining and crushing of iron ore is another occupational source of iron exposure (22). High concentrations of emery dust have been reported during the manufacture of emery cloth and papers, in the setting up of polishing wheels, mops, and abrasive paste, and as a wear-resisting component of concrete floors. Emery consists of fine crystals of aluminum oxide embedded in a matrix of iron oxide. It is an impure variety of the mineral corundum (Al_2O_3) which, next to diamond, is the hardest natural mineral known. Mining, pulverizing, and mixing natural minerals such as hematite, limonite, and magnetite may result in significant exposures (16)(20). Siderosis

may occur in workers who pulverize and mix natural pigments or prepare synthetic pigments (23).

Epidemiology

Prolonged inhalation of fumes originating from melting or boiling iron materials during arc welding or oxyacetylene cutting may result in siderosis (5-8)(11-13). In some reported cases, clinical impairment and abnormal pulmonary function tests have been reported (22). Silver polishers (1)(19), iron ore workers (9)(15)(22)(27), workers exposed to emery dust (2), foundry workers (11), magnetite workers (16)(20) and others (25) may develop siderosis secondary to prolonged exposure to various iron-containing materials. In general, pulmonary fibrosis occurs only when there is an associated fibrogenic dust component, such as silica, also present in the work environment (See section on mixed dust pneumoconioses).

Estimate of Population at Risk and Prevalence of Disease

NIOSH estimates approximately 5 million individuals are currently exposed to iron and iron compounds (28). This includes approximately 2,700 iron ore miners and more than 4 million other workers exposed to iron oxides. The prevalence rate for siderosis among welders was reported to be 17.6 per hundred in a survey at a Sheffield steel foundry (11). The mean age of disease onset was 46.4 years with the majority of cases occurring in individuals 40 years of age and older; cases were also reported in workers less than 35 years of age. In the same study, the mean onset age for silicosis was 52.2 years. Average years of exposure was 21.9 years for welders with siderosis, 31.7 years for workers with silicosis, and 33 years for individuals with coal workers' pneumoconiosis. Hunnicutt, et al. reported x-ray changes occurred in 34% of electric arc welders (14). Data on prevalence of disease is not available for other occupational causes of siderosis.

Pathology

In the pure form of siderosis, gross pathologic examination demonstrates no obvious underlying fibrotic disease. The visceral pleural surface is rust or brick-red in color. The lung, when cut, has a brownish surface on which are superimposed darker macular areas 1-4 mm in diameter. In some areas it is difficult to identify individual macules, many appearing to blend

together or with surrounding pigmented lung tissue.

Microscopically, iron particles are seen to accumulate mainly around small vessels and bronchioles. When the dust burden is large many alveoli may be completely filled with brown pigmented macrophages containing iron. Iron may also lie free within alveolar spaces. There may be a slight reticulin response to the dust, but even in the presence of large quantities of iron pigment, fibrosis is notable by its absence (23).

Hematite Miner's Lung

Lung disease has been particularly prevalent among hematite miners since the introduction of the pneumatic drill in 1913. Hematite pneumoconiosis results from the inhalation of dusts from pulverized siliceous rock containing both iron and free silica particles (26). Stuart and Faulds divided the hematite lung into three pathologic types: diffuse, nodular, and massive fibrotic (27). The diffuse variety is characterized by a brick-red colored lung surface with superimposed darker dust foci and surrounding centrilobular emphysema. It has been likened to the simple form of coal workers' pneumoconiosis (26). The nodular type is characterized by dark, reddish-black fibrous nodules up to 1 cm in diameter located primarily in the upper zones of the lung. Thickening of the pleura was noted in many cases. Microscopically, the lesions have a concentrically whorled collagenous center surrounded by iron containing macrophages and thus closely resemble silicosis. The lesions of massive fibrosis in hematite lung are similar to those seen in coal workers' pneumoconiosis and silicosis. They are usually confined to the upper lobes and have sharply demarcated borders. Dense pleural adhesions are common and the fibrotic mass may encroach and obstruct pulmonary vessels and bronchi.

In general, the greater the amount of pulmonary fibrosis, the greater the lung tissue silica content (9).

Other Pneumoconioses Characterized by Heavy Exposure to Iron Containing Dusts

A type of pneumoconiosis has been described in lungs of silver polishers exposed to large amounts of iron oxide (rouge) in polishing material. The lesions included massive fibrosis despite the absence of silica in the dusts (1)(26). Pulmonary lesions have also been described in other workers simulating nodular silicosis, with

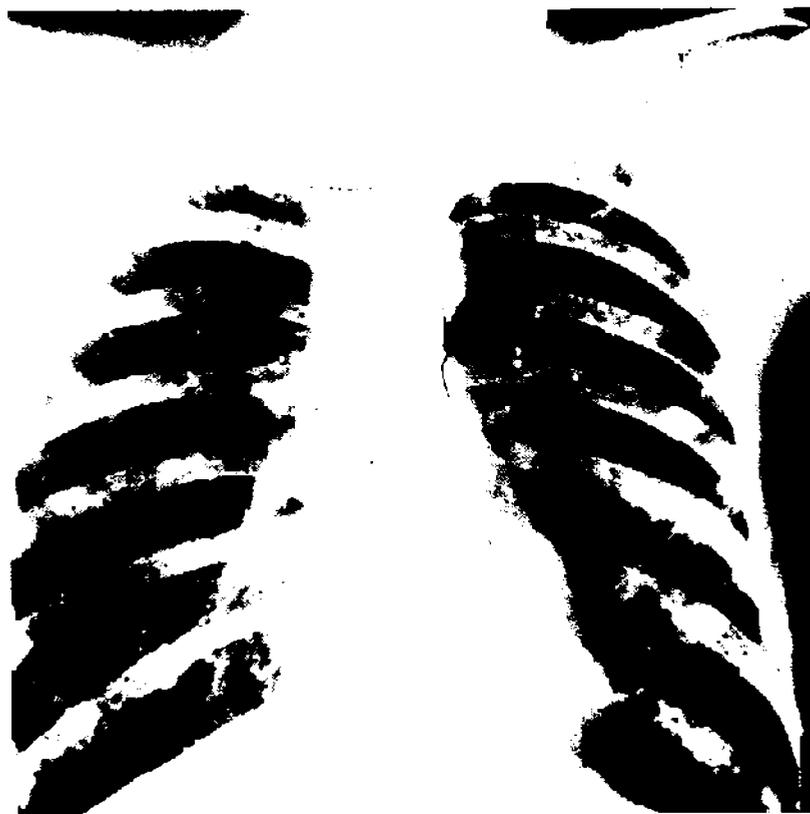


Figure II-44

Source: Morgan and Kerr (21).

extensive fibrosis and necrosis (25).

A number of investigators have described postmortem changes in electric arc welders (5)(6)(8)(12)(13)(17)(18). On gross examination, the lungs are dark and appear anthracotic. Microscopically, the perivascular and subpleural alveoli are filled with macrophages loaded with coarse black granules of iron oxide. In the majority of cases examined, pure iron oxide alone was not thought to be responsible for the fibrosis (7)(13). X-ray changes noted in arc welders are caused by radiodense iron-oxide deposits within alveolar, septal, and perivascular walls.

Morgan and Kerr obtained lung biopsies in four welders with siderosis (21). There was an absence of fibrosis despite the presence of large amounts of iron in the distal air passages and lymphatics. The iron content of lung tissue was reported to be 15 to 20 times greater than normal values. It appears that the nodular x-ray appearance resulted from the deposition of iron in the perivascular lymphatics (see Figure II-44).

Levy and Margolis reported a case of a gas-

torch cutter with siderosilicosis, diffuse interstitial fibrosis, and highly atypical alveolar epithelium (17). Studies of lung tissue from an autopsy of a 58-year-old arc welder with arc welder's pneumoconiosis emphasized the diagnostic usefulness of scanning electron microscopy combined with backscattered electron imaging and x-ray analysis for *in situ* identification of mineral dusts (12).

Clinical Description

Diagnosis is largely dependent on obtaining an appropriate occupational history, demonstrating airborne iron dust in the work environment, and obtaining a chest x-ray compatible with the findings of siderosis. The worker is rarely symptomatic and usually is unaware of his disease until the chest x-ray is obtained. The changes noted on x-ray may be difficult to distinguish from simple silicosis (22). Nodular opacities are well circumscribed but may appear more radiodense than typical silicotic nodules. Aggregation of nodular shadows does not occur, and the x-ray shadows may resolve if there is no

further exposure to iron oxide dust. Pulmonary function tests are rarely abnormal (22).

Diagnostic Criteria

Diagnosis is dependent upon an appropriate occupational history which documents the iron oxide dust and the characteristic chest x-ray findings. The recent application of magnetopneumography to the study of the pneumoconioses may be a valuable tool for the documentation and quantification of ferromagnetic mineral dusts in human lungs (10).

Methods of Prevention

The siderosis that occurs in welders is usually seen in those individuals who work indoors in poorly ventilated workrooms. Exposure can be reduced by proper ventilation or by having the employees work outside. In general, control of dust levels requires the same procedures and techniques described for silica.

Research Needs

More sophisticated physiologic testing, including measurement of the lung's mechanical properties, is required to better document lung function changes that may occur following inhalation of iron-containing dusts. *In vitro* studies or animal experimentation might be helpful in determining dose-response relationships, understanding lung clearance mechanisms for iron, and elucidating any fibrogenic properties of various ferrous compounds.

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SILVER

Introduction

Silver (Ag) is a white, very malleable and ductile metal which is classified as a precious metal. The chief effect of excessive silver absorption is argyria, the local or generalized impregnation of tissue with silver. This normally does not produce a recognizable disturbance of health. The inhalation of dust containing silver may result in pathologic changes by combining with proteins in the lung and causing the elastic tissue to be stained black. Because of this, silver is regarded as a form of pneumoconiosis, although

no clinical, physiologic, or x-ray changes occur in individuals exposed.

List of Causative Agents (Manufacturing Processes)

Silver is present in many ores, the most important being argenite (Ag₂S). It is estimated to be present in the earth's crust in amounts of about 0.1 gm per ton (3). Copper, lead and zinc ores frequently contain small amounts of silver. In fact, about 70% of all production of silver is a by-product of the refining of these metals. Mexico and the United States produce more than half of the silver in the world (2). Nearly 99% of the silver is produced in Arizona where it originates from copper ore; most silver produced in California is a by-product of gold quartz mining.

Silver can be extracted from ores by a cyanide process in which the crushed ore is ground into cyanide solution, the resultant pulp agitated by jets of compressed air, and the silver precipitated by the addition of a zinc dust emulsion (3). A second method is based on the greater affinity of zinc than lead for silver present in lead-silver ores. There is also an electrolytic process where silver is recovered from the anode slimes obtained in electrolytic lead refining (3).

Because silver is such a soft metal, it is not normally used in industry in its pure state; it must be alloyed with a hardener, usually copper. Sterling silver is the name given to a standard high-grade alloy containing a minimum of 925 parts silver per 1,000.

List of Occupations and Industries Involved

Silver has many uses including: the manufacture of silverware and jewelry; in alloys with copper to increase strength and hardness; with aluminum in the manufacture of scientific instruments; with cadmium and copper in automobile bearing alloys; with lead to increase corrosion-resistance to sulfuric acid; with lead and antimony in grids for storage batteries; and with chrome-nickel and steels, especially steel dies (3). It is also used in solders and brazing alloys; as bearing linings in air-cooled aircraft engines; in manufacturing pipes and valves; in pasteurizing coils and nozzles; in milk, cider, and brewing trades; in the acetate rayon silk industry; in application of metallic film in glass and ceramics; as an electroplated undercoating for nickel and chrome; in photography; and as a bactericide (3). Jewelers' rouge is used for polishing and the dust

generated during polishing consists of silver and iron oxide particles (9). Silver is also used as busbars and winding in electrical plants, in dental amalgams and as a chemical catalyst in the synthesis of aldehydes (10). Some of the compounds are of medical importance as antiseptics or astringents and in the treatment of certain diseases, particularly in veterinary medicine.

Some occupations in which exposure may occur include:

- alloy makers
- ceramic makers
- chemical laboratory workers
- drug makers
- food product equipment makers
- hair dye makers
- ivory etchers
- organic chemical makers
- silver polishers
- bactericide makers
- coin makers
- dental alloy makers
- electric equipment makers
- glass makers
- hard solder workers
- mirror makers
- photographic workers
- water treaters

Epidemiology

There are only individual cases of argyria reported and only limited epidemiologic studies.

Estimate of Population at Risk and Prevalence of Disease

There are probably too few workers to provide any estimate of any accurate prevalence or population at risk, although estimates from census data and disease prevalence studies suggests that there are potentially 60,000 exposed workers.

Pathology

No human pathological material has been adequately described. Implantation of small silver particles into the skin may cause permanent skin discoloration (10). Silver nitrate dust can cause skin irritation, as well as conjunctival burns leading to blindness (10). There may be resultant pigmentation of the skin, eyes, nasal

septum, and tonsillar pillars. Once silver enters the body, very little is excreted (10). Studies on the occurrence of argyria following injection of silver arsphenamine reveals development of observable disease with a total dose of 0.9 gms of silver (10). Argyria may develop in workmen who inhale or handle silver oxides or salts (nitrate, fulminate, or cyanide) (10). In workmen who are affected, there are no constitutional symptoms, but there may be permanent pigmentation of skin and eyes. When biopsies of nasal or bronchial tissue have been made, tissues have been found to be heavily laden with particles of silver salts which have also been noted to be scattered along lymphatics (3). Additionally, the bronchial mucous cells have revealed basal membrane deposits.

The inhalation of metallic silver by silver finishers using "rouge" (an iron oxide) caused a fine granular pigmentation of the elastic fibrils in the alveolar walls (7). Hardin described a 63-year-old man who spent all of his working life as a silver finisher (6). At autopsy, histology sections of lung tissue showed some subpleural and periarterial fibrosis. A great deal of pigment was present in and around the areas of fibrosis, some within alveoli. There were perivascular aggregates that showed no fibrosis. Incinerated sections of lung tissue showed that most of the pigment was iron, but with silver deposited on elastic laminae. The amount of silica seen by polarized light was small and appeared to be no more than in normal controls. Chemical examination of lungs show that ash constituted 8.38%; iron (Fe_2O_3) 3.5%; total silica 0.22%; free silica nil; and silver (as metal) 0.36% of the dry weight (6). It was suggested this worker was particularly sensitive to the presence of the inhaled iron oxide which caused the pulmonary fibrotic changes. However, the amount of fibrosis in the lungs was small and the fibrotic areas, noted only on microscopic examination, were well separated.

There have been other reports of silver finishers in which heavy loading with iron oxide was not accompanied by pulmonary fibrosis (1)(7). Furthermore, iron oxide used in the finishing of silver and silver-plated articles did not produce fibrosis in the lungs of experimental animals (3)(4)(5).

Clinical Description

There are no clinical signs, symptoms, or specific chest x-ray findings that result from the

inhalation of silver. Diagnosis is made by occupational history and by noting the discoloration that may occur on the skin and mucous membrane of conjunctiva. Characteristically, the workmen's faces, hands, and arms develop a dark slate-gray color which is uniform in distribution and varies in depth depending on the degree of exposure. There may also be discoloration of the fingernails, bronchial mucosa, and toenails. Covered parts of the body are affected to a lesser degree by the discoloration process (10). Dust may be deposited in the lungs and produces no fibrosis. There is no specific treatment for this condition.

Diagnostic Criteria

Diagnosis depends on an occupational history and the presence of skin, mucous membranes, and conjunctiva discoloration. Chest x-ray is not abnormal. Urine silver analysis is not helpful because very little silver is excreted in the urine. Argyrosis of the respiratory tract with generalized argyria has been described in two men who were employed in the manufacture of silver nitrate (8). There were symptoms of mild chronic bronchitis, but there was no discoloration of the skin, eyes, or mouth. Nasal mucosa showed bilateral symmetrical dark pigmentation of the walls of the middle and upper regions. In the more severe case, bronchoscopy showed isolated plaques of pigmentation at the tracheo-bronchial bifurcation and uniform zones of greyish-yellow coloration around the orifices of the smaller bronchi, but the intermediate bronchi remained free. Biopsy of the nasal or bronchial mucous membrane demonstrates deposition of silver.

Research Needs

More studies are necessary, but may be limited because of the cost of conducting animal experimentation.

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MIXED DUST PNEUMOCONIOSES (Iron and Other Compounds and Silica)

Introduction

Mixed dust fibrosis—a term first coined by Uehlinger in 1946 and adopted by Harding, Gloyne, and McLaughlin in 1950—is applied to pulmonary lesions caused by the inhalation of silica dust (or a fibrogenic dust) in combination with other (usually nonfibrogenic) dusts (7). Mixed dust fibrosis does not include lung disease which occurs when the dusts are inhaled separately and at different times. In the majority of instances, dusts of iron or its compounds are inhaled along with silica. The term nonferrous refers to alloys containing a copper (brass, bronze, and gunmetal), aluminum, or magnesium base.

List of Causative Agents (Manufacturing Processes)

Mixed dust pneumoconioses occur in industries where there is exposure to dust combinations. This includes crystalline silica in combination with nonfibrogenic dusts; iron and iron products; and brass, bronze, aluminum, or other nonferrous alloys.

List of Occupations and Industries Involved

Mixed dust pneumoconioses occur in industries where there is exposure to both free silica and to iron or iron products. This includes iron, steel, and nonferrous foundries; hematite mining; cleaning and scaling of boilers; electric arc welding and oxyacetylene cutting (when concomitant exposure to silica dust is present); and potteries (14).

Epidemiology

Steam-driven ships periodically require docking in order to have their boilers sealed and cleaned. Men employed full time in this occupation must work in confined spaces, crawling along with lamps and hammers, chipping off scales as they go, and often working in a hot atmosphere (8). Considerable amounts of dust are created from the breaking off of scales deposited in the boilers and from flue dust in the fire tubes originating from the use of coal and other fuels. Silica content of flue dust has ranged between 6.1% and 26.4% (3)(10). Pneumoconioses has been reported in these workers (8).

Brass and bronze molders and casters working with sand molds may inhale mixtures of dust sand fumes (9). The sand that is used has a lower free silica content (about 80%) than the sand used for steel casting (about 95%), because the temperatures used for nonferrous metals are lower than those used for steel and iron and the melting temperatures are different. Fettlers who remove burnt-on sand from castings have significant dust exposures. High levels of dusts are also generated during the application of parting powders and molding dress, exposing molders and casters who perform this work. Before 1950, parting powders had high silica concentrations (9). There are other exposures including dusts and fumes of various metal oxides including zinc, tin, and lead. It has been reported that mixed dust fibrosis occurs sooner in iron fettlers than brass fettlers because the melting temperature of iron is higher than that of brass and there

is, therefore, more burnt-on sand found on iron castings (9).

Estimation of Population Exposed

The 1976 Metal Casting Industry Census Guide reported that there were 4,938 foundries in the United States employing 490,000 people with a total capacity for producing 33,700,000 tons/year of ferrous and nonferrous castings (5). Of the large numbers of foundry men casting ferrous alloys, almost half of them worked in foundries employing 100 and 500 people, while the majority of nonferrous foundry men worked in foundries employing less than 100 people (5).

Pathology

In mixed dust pneumoconioses, the gross appearance of the lungs reveals a thickened pleura, possibly with evidence of underlying fibrotic masses and occasionally bullae. On sectioning the lung, punctate, irregular, or stellate-shaped areas of fibrosis are noted which vary in size from 3-4 mm. Occasionally larger and more confluent masses are seen, but typical silicotic nodules are not seen. When changes similar to progressive massive fibrosis occur, the lesions are pigmented brick-red color in contrast to the black-pigmented lesions of coal workers' pneumoconiosis. The varying sized lesions are more numerous in the upper lobes.

On microscopic examination, particles of iron and silica are identified accumulating within alveolar walls and adjacent to respiratory bronchioles and small arterics. (Also see Pathology section of Siderosis chapter page 423.) The amount of pulmonary fibrosis occurring seems to be determined by the amount of quartz present. Fibrotic lesions are seen surrounding bronchioles and small vessels. There may be obliteration of surrounding alveoli. Individual fibrotic lesions are irregular in shape, perhaps stellate-shaped, and are not concentrically nodular such as seen in silicosis. The lesions have a characteristic "Medusa head" picture (14). When silicotic nodules are present, the nodular components are said to appear immature (14). In addition to quartz dust, carbon, iron, and other metallic dust particles are present in large quantities within lung tissues. When progressive massive fibrosis lesions occur, they contain a great deal of dust which is randomly arranged and extra-cellular in location (4)(13)(14). Contraction and distortion of tissue may produce irregular emphy-

sematous scars and bullae. In hematite miners, the lung tissue contains hematite, silica, and mica (4)(14). Silica makes up perhaps 4% of the total dust with greater quantities noted in lungs containing more fibrosis (4).

Mixed dust fibrosis appears to be a modification of the effects of small quantities of free silica by the accompanying nonfibrogenic dust. Iron oxides, for example, have been shown to inhibit the fibrogenic effects of quartz (11). Hematite produced no fibrosis when administered to experimental animals (1). Organic iron (as ferritin) engulfed by alveolar macrophages may shorten a cell's life and cause disruption of the cell and release of collagen-stimulating substances (2). It is not clear whether iron influences collagen formation but, experimentally in mixtures, it inhibits the fibrogenic potential of quartz (14).

Nagelschmidt examined 144 lungs with mixed dust fibrosis and reported that the concentration of iron oxide per pair of lungs varied between 9-45 gms (13). The average lung dust composition was approximately 80% hematite, 5% quartz and 15% mica. The amounts of dust found in the lungs with massive fibrosis ranged between 30-85 gms, perhaps two to three times as high as the dust content of the lungs of coal miners. Gerstel found that the total iron oxide content of the lungs of silicotic coal miners, lead and zinc miners, iron ore miners, and ceramic workers ranged between 0.4-5 gms (6). In some cases of fibrosis there may be as much as 100 gms of dust with little or no silica (13).

In order to demonstrate the relationship between the total dust and quartz concentration, Nagelschmidt plotted the average amount of quartz against the average amount of total dust in lungs of individuals who died with pulmonary fibrosis (13). Included were coal miners, foundry workers, hematite miners, and quartz-free massive fibrosis.

Mixed dust fibrosis accompanied by areas of focal emphysema are common findings in nonferrous (mainly brass) foundry workers as well as iron and steel foundry workers (9). Whorls of silicotic nodules are occasionally found. There is a rough correlation between the percentage of free silica present and the amount of fibrosis.

Clinical Description

The clinical picture of mixed dust fibrosis is similar to that found in nodular silicosis.

Nodular opacities appear on chest x-rays resembling silicosis or coal workers' pneumoconiosis. When larger opacities occur, they are usually found in upper and mid zones and may, on occasion, be confused with tuberculosis. Large, well-circumscribed opacities similar to conglomerate masses in complicated silicosis rarely occur. Calcification does not occur in lesions unless caused by tuberculosis and egg-shell calcifications of hilar lymph nodes are seen. Small radiodense opacities may also be present in iron foundry workers or occupations where iron dust is inhaled (7)(12)(14).

In siderosis, as in nonfoundry welders, silver finishers, etc., aggregation of nodular shadows is not seen (12). The x-ray shadows even resolve if there is no further exposure to iron oxide dust (16). By contrast, in mixed dust fibrosis, when nodular shadows are seen, the lesions may coalesce and remain even if workers are removed from exposure.

Diagnostic Criteria

Diagnosis is dependent upon an appropriate occupational history which documents the mixtures of dust, especially iron and silica, and the characteristic chest x-ray findings.

Prevention

This is much the same as in silicosis.

Research

Well controlled epidemiologic studies accurately documenting environmental dust mixtures are needed. Animal and *in vitro* studies comparing the effects of ferrous and nonferrous materials on the fibrogenic properties of silica seem appropriate. Newer developments in alveolar macrophage technology would allow proper investigations of the effects of mixed dusts on these cells.

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MISCELLANEOUS PULMONARY REACTIONS

Bakolite Pneumoconiosis

Bakolite is a phenolic plastic obtained by the polymerization of phenol and formaldehyde by heat and pressure (17). It has multiple industrial uses, but is particularly used in electric and telephone equipment. There are several reports of nodular chest x-ray changes occurring in workers exposed to bakolite dust along with other organic dust (1)(17). Pulmonary granulomatous lesions have been reported in two workers exposed to bakolite dust (17). One was a cabinet maker exposed to bakolite dust during a polish-

ing procedure of exotic wood for three years; the second was exposed for 15 years to bakolite objects used for electrical appliances. Chest x-ray showed bilaterally diffuse mottling and enlarged hilar lymph nodes. One case showed evidence of interstitial fibrosis. On pathological examination there were sarcoid-like granulomas noted. The granulomas were characterized by intracellular inclusions which gave a positive chemical reaction for phenol compounds. In an animal model, pulmonary fibrosis was noted to develop (17). Further studies are necessary in order to determine the significance of these findings.

Manganese

Manganese is a silvery-white metal but as usually prepared is reddish-gray in color, brittle, and intensely hard. The most important ore is pyrolusite or black dioxide (MnO_2). Less important manganese minerals include: braunite, Mn_2O_3 , H_2O and hausmannite, Mn_3O_4 . It also occurs as a sulfide (hausserite) in a manganese blend; as a carbonate in managesestat; and as a silicate in tebhrorite, kneblite, and rhodomite (6).

Manganese is widely distributed in the earth's crust and is calculated to be the twelfth most abundant element (25). Chief countries supplying ores are Russia, India, South Africa, Ghana, Brazil, and Morocco. The ores found in the United States are of low grade quality (6). The mining of manganese can result in significant dust exposure, particularly during drilling with pneumatic drills (25). Grinding of ores is responsible for a great number of manganese poisoning cases (25).

Manganese is used in steel manufacturing and as a part of alloys with copper, aluminum, magnesium, and iron. More than 90% of the manganese used in the United States is found in the production of steel and iron (25).

Poisoning has been reported to occur among workers making ferromanganese alloys; during crushing and screening of ferromanganese; and among arc welders burning steel containing low concentrations of manganese (25). Crane operators in a vicinity of manganese ore smelting may also be affected. Manganese dioxide ores are used in the chemical industry for the production of hydroquinone, potassium permanganate and manganese sulfate. Manganous oxide (MnO) is added to animal and poultry feed. Dry-cell batteries use manganese dioxide as a depolarizer in a cell

for the readily obtained oxygen it contains. Cases of poisoning have occurred among workers in the dry-battery industry (8). Chemicals containing manganese are used in the ceramics industry to color glass, face brick, and ceramic products. Welding rods and fluxes contain manganese. Manganese dioxides and other compounds are used in the manufacture of dyes, paints, varnish, dryers, fungicides, and pharmaceuticals. Manganese compounds may be added to chemicals used as smoke inhibitors, as additive to fuels, and as oil and anti-knock additives to gasoline supplementing lead anti-knock compounds.

It has been estimated by NIOSH that approximately 168,000 workers are exposed to manganese compounds (26).

The two major toxic pathologic effects of manganese relate to a chronic central nervous system disorder similar to Parkinson's disease and manganese pneumonia. In the early part of the century, Brezina reported 5 cases of death from pneumonia among 10 manganese workers in an Italian pyrolusite industry in 1929 (25). An epidemic of lobar pneumonia was reported from Norway in 1939 (25). Smoke from a ferromanganese smelting plant containing silica and manganese oxides polluted a town. During the year with heavy pollution, lobar pneumonia accounted for 32.2% of all deaths in the community. Corresponding figures for all of Norway were 3.65% (25). The incidence of pneumonia among men exposed to manganese oxide dust as part of the manufacturing of potassium permanganate was 36 times higher than an unexposed comparison group (14). Confirmation of human studies is born out by inhalation studies of mice which reveal that manganese is toxic to respiratory epithelium and produces an intense interstitial inflammatory response (14). Studies on guinea pigs also confirm that the toxic effect of manganese dioxide dust might augment concomitant respiratory infections (28). Manganese, in combination with *Candida albicans*, caused pulmonary fibrosis (28). However, exposure to MnO₂ dust did not significantly affect rat lung enzymes or microsomal fractions even though manganese was significantly increased in tissues remote from the lung (indicating translocation of dust from intrapulmonary locations) (21).

In acute manganese pneumonia, symptoms are similar to other types of pneumonia. There are no characteristic pulmonary function or x-ray changes. Diagnosis depends on careful oc-

cupational history and appropriate clinical picture.

Polyvinyl Pyrolidone (Thesauriosis)

Individuals exposed to hair lacquer sprays may develop a lung disease known as thesaurosia. There are three basic types of hair sprays. These include polyvinyl pyrrolidone (p-type) where PVP is combined with trichlorofluoromethane and dichlorofluoromethane as aerosol propellant in metal dispensers; shelactite made of dewaxed shellac mixed with castor oil in some sort of aerosol propellant in metal dispensers; and a mixture of the two (16). Workers most likely to be affected are beauticians or hairdressers. However, men and women using or children playing with hair sprays may also be exposed.

Disease attributed to hair sprays have included interstitial fibrosis, hilar adenopathy, and sarcoid or foreign body-type granuloma (2)(3)(9)(15). PAS positive intracytoplasmic granules have been identified within macrophages, lung tissues, and lymph nodes (3). However, similar staining granules have been reported in sarcoid and other granulomatous diseases. Chemical analyses of lung tissue have not demonstrated PVC which is readily soluble in water and chemically inert (16). It has been suggested that lubricants in PVP or in the mixed sprays cause the pulmonary lesions and not the PVP itself (7).

X-ray surveys performed on a large number of hairdressers have not demonstrated any significant pulmonary disease ascribable to sprays (10)(12). In cases where lung disease has been reported, the average duration of exposure before diagnosis of disease was approximately 2.9 years, ranging from six months to eight years (9). The youngest patient was eight years of age (9). Symptoms described were nonspecific and included exertional dyspnea, cough, and occasional fever. Chest x-rays revealed patchy or linear opacities; occasionally hilar lymph nodes were enlarged (9). When sprays were discontinued, chest x-rays have shown clearing of lesions within six months, but in a few it has taken as long as two years (9).

Titanium

Titanium, present in a variety of minerals, is an abundant element. It is considered rare because it is difficult to separate. It is used as ferrotitanium for deoxidizing and denitrogeniz-

ing steel and in alloyed steel to increase tensile strength, toughness, and hardness. In chromium steel it minimizes intergranular corrosion (4). Titanium oxide is used as a paint pigment while titanium tetrachloride has been used for making smoke screens and for skywriting. Titanium tetracarbide is used with tungsten carbide for the manufacturing of tools (5). There is one report that titanium oxide may cause radiographic changes, similar to those seen following inhalation of iron or tin, without functional impairment (20).

Vanadium

Vanadium is obtained by roasting the ores from the thermal decomposition of iodide or petroleum residues, from slags resulting from ferrovanadium production, or from soot obtained by oil burning (24). Because high temperatures are necessary and vanadium has a tendency to reoxidize, pure vanadium is difficult to obtain, even on a small scale (11). Vanadium is found in combination with other elements in rocks and some petroleum deposits because the blood of certain fossilized remains consists in part of vanadium (16).

Vanadium ore is crushed and dried and then finely ground and roasted. After mixing with sulfuric acid, the resulting precipitate is dried as vanadium pentoxide and packed in bags. Roasting and bagging processes produce the most dust; grinding and crushing produces less (16).

Vanadium is used in the steel industry because of its powerful oxidizing capacity, ability to increase hardness, malleability, and resistance to fatigue. It is used as a catalyst in the manufacture of phthalic anhydride and sulfuric acid and in the oxidation of ammonia and nitric acid. Vanadium is used for the manufacture of dyes and inks, paints and varnish dryers, insecticides, and in photography. Animal studies indicate the pulmonary effects of vanadium are primarily irritant in nature (18)(19). Animals exposed to vanadium dusts develop profuse mucoid nasal discharge, sneezing and wheezing, bronchitis, and bronchopneumonia. Dust accumulates within cells and there may be some interstitial fibrosis (18). In humans, the irritative nature of vanadium causes bronchitis symptoms, and conjunctival and nasal irritation (5)(13)(22)(23)(27) (29). Acute bronchospasm may develop when high concentrations of vanadium dusts are present. Although

the radiodensity of vanadium is less than that of iron, there is no evidence that it causes x-ray changes. This may be due to its rapid absorption from the lung (16).

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TIN

Introduction

Tin is a soft, malleable metal slightly harder than lead. It is resistant to atmospheric corrosion and it may be dissolved in mineral acids (4). It is used to make brasses, bronzes, and babbitts, and in soft solders. It is more radiopaque than iron, and when inhaled and deposited in the lungs, it produces dense x-ray shadows, a condition known as stannosis.

List of Causative Agents (Manufacturing Processes)

Next to gold and copper, tin is the earliest metal known to man (20); it was first obtained from ores about 5,000 years ago (10). Tin smelting probably began in northwest Persia about 1600 B. C. (10). It was soon discovered that copper, combined with tin, produced an alloy that was stronger and easier to cast in a mold and thus was preferable for weapons production. The bronze age began in Egypt 1,000 years before spreading to northern Greece but occurred in Great Britain between 1800 and 1600 B. C. (15). Tin was known to Homer between 900 and 750 B. C.; in the "Iliad," Agamemnon's shield had 20 knobs of tin making a circle around the dark enamel boss (17).

Cassiterite (SnO₂) is the primary ore from which tin is obtained. An important use of tin is providing a protective coating for other metals, particularly in the food and beverage canning industry, roofing tiles, silverwares, coated wire, household utensils, electronic components, and pistons. Electroplated tin provides a durable protective finish and produces a lubricating effect on bearing surfaces (4). Common tin alloys are phosphor bronze, light brass, gunmetal, high ten-

sile brass, manganese bronze, die casting alloys, bearing metals, pipe metals, and pewter (23). Tin is used for solder, fillers in automobile bodies, castings for hydraulic brake parts, aircraft landing gear, and engine parts. Metallic tin is used in the manufacture of collapsible tubes and foil for packaging. Organic and inorganic compounds are used in the production of drill-glass ceramic, porcelain, enamel, glass, and inks. They are also used as a mordant in production of fungicides, anthelmintics and insecticides, and as a stabilizer polyvinyl plastics and chlorinated rubber plants and in plating baths (23). Stannous chloride is used in the chemical industry as a reducing agent, for immersion, tinning of metal, and for sensitizing glass and plastics before metalizing. Tin oxide is used as a opacifier in ceramic enamels, as a ceramic color, as an abrasive, and as a coating for conductive glass. The term organotin refers to butyl compounds which are used as catalysts, or heat and light stabilizers, in vinyl polymers and chlorinated latex paints. Tins in paints act as stabilizers to prevent darkening (9).

List of Occupations and Industries Involved

Exposure to tin occurs during mining, smelting, refining, and in production and use of tin alloys and solders. Occupations in which exposure to tin may occur include: (23)

- Babbitt makers (tin-copper)(antimony)
- Britannia metal workers (tin-copper-antimony)
- dye workers
- pewter makers
- textile workers
- Herth tanners
- valuing of tin oxide (detinning furnace tender)
- brass founders (copper and zinc)
- bronze founders (tin-copper)
- fungicide workers
- pigment workers
- solder makers
- type metal makers (lead-antimony tin)
- scrap metal recovery plant operators
- tin miners

The amount of tin in crude ore is so small that mining procedures involving drilling and

loading of ore do not cause stannosis. The silica in the dust, however, may cause silicosis (13). Tin dust and fumes are generated when emptying bags of crude ore into ships, and in the milling and grinding of ore (12); shoveling of split ore, tipping of crushed ore into calcination furnaces; charging smelting furnace with calcined ore producing tin oxide fumes (21); shaking out of the refinery furnace which contains high percentages of tin oxide; melting down tin scraps in order to recover tin oxide (7); and in procedures where material to be plated is dipped by hand into molten tin (5).

Epidemiology

Pendergrass and Pride reported a 45-year-old man whose job consisted of bagging tin oxide for a period of 15 years (14). Abnormalities on chest x-ray were noted during a routine survey but the worker complained of no symptoms or disability. Bartak and Tomecka (2), described an enamel factory worker who charged furnaces in which tin was converted (burned) to tin oxide for 18 years. He complained of no symptoms and demonstrated no abnormal physical findings. Chest x-ray showed diffusely scattered radiodense shadows. In the same factory, 6 of 16 co-workers showed similar x-ray findings. These individuals were exposed to tin oxide dust for periods ranging between 6 months and 25 years. Robertson and Whitaker reported chest x-ray changes suggesting pneumoconiosis in 121 of 215 workers in a tin refinery who did not demonstrate clinical findings (19). Cutter et al. described two cases with x-ray findings showing nodules 1-2 mm in diameter not accompanied by any pulmonary dysfunction (6). A report of the autopsy findings of an asymptomatic tender of a detinning furnace revealed concentrations of tin in his lungs of 110 mg per 100 gms of wet lung tissue which was approximately 2,000 times the normal value (7). X-ray defraction analysis confirmed that tin oxide was the only metal or mineral present. Cases reported by Spencer and Wycoff, Robertson and Whitaker, and Oyanguren had no disability but abnormal chest x-rays (11)(19)(21). Dundon and Hughes suggested that tin fumes were a more important source of exposure than tin oxide dust (7). However, studies by Robertson and Whitaker suggested that the two most important factors in causing lung deposition were the quality of the dust and duration of exposure (19).

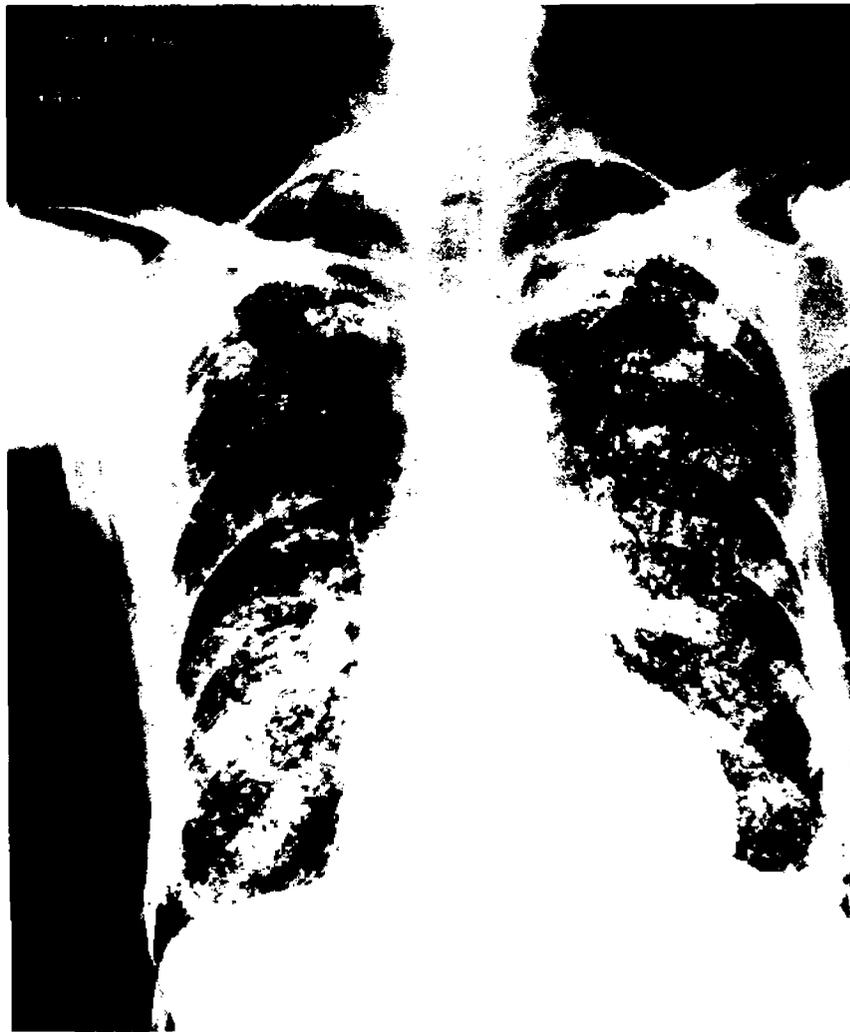


Figure II-45.

Estimate of Population at Risk

Stannosis seems to be an uncommon cause of pneumoconiosis with only approximately 140 recorded cases (13). However, NIOSH estimates that there are perhaps 250,000 workers exposed to tin or tin oxide.

Pathology

Examination of the cut surface of the lung reveals numerous 1-3 mm size gray-black, rounded densities scattered throughout the lung tissue (13). They are primarily located in the subpleural area and in interlobular septal tissue (22).

On microscopic examination, macrophages

containing dust particles are deposited within alveolar walls, around vessels and bronchioles, and beneath the pleural surface. Aggregations of dust particles accumulate in hilar lymph nodes. The dust-laden macrophages aggregate around the perivascular and peribronchiolar tissue producing macules which are similar to those seen in coalworkers' pneumoconiosis and siderosis (13). Massive fibrosis does not occur and little reticulum or collagen fiber formation develops. The dust does not cause bronchitic changes. No appreciable chronic lung changes such as emphysema or fibrosis have been observed (22), even after 50 years of exposure to tin oxide (18).

Tin oxide crystals are strongly birefringent in contrast to silica which is poorly birefringent.

X-ray diffraction analysis provides definite identification of the pigmented particles. Following microincineration of lung tissue, carbon particles disappear while tin particles remain. Tin concentrations in lung tissue in stannosis cases have been reported to range between 0.5 and 3.3 gms per lung, in cases where duration of exposure has been 11 and 50 years (18). There is a good correlation between the quantity of tin in the lung and x-ray changes (18). Tin oxide does not cause lung fibrosis in experimental animals (8)(16).

Clinical Symptoms

Tin pneumoconiosis or stannosis was first described by Beintker in 1944 (3). There are no reported symptoms or abnormal findings on physical examination. Pulmonary function tests usually are normal. Chest x-ray appearance may resemble siderosis. Following heavy prolonged exposure to tin oxide dust, many small, dense radiopacities develop and are scattered relatively evenly throughout lung fields (13)(see Figure 11-45). Opacities are usually 2-4 mm in size, somewhat irregular in outline and extremely radiopaque. In the upper lung zone, dense linear opacities may be seen and Kerley B-line may be seen throughout the lungs (13). Exposures that are less intense produce fewer and less dense opacities on chest x-ray. Large confluent opacities and hilar adenopathy do not occur.

Diagnostic Criteria

Diagnosis is made by obtaining an occupational history of significant tin exposure, lack of clinical symptoms and physical findings, and the presence of very radiodense opacities on chest x-ray. In the absence of a history of exposure and when opacities are few in number, the pneumoconiosis may be mistaken for siderosis and possibly silicosis. X-ray diffraction analysis of lung tissue may provide definite identification.

Prognosis

Stannosis has no known effect on health or life span. It has not been well documented whether termination of exposure results in gradual disappearance of the x-ray opacities.

Methods of Prevention

Prevention depends mainly on efficient dust suppression, good exhaust ventilation, and good factory housekeeping. Tin oxide is classified as

an inert or nuisance particulate by the ACGIH (13).

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TUNGSTEN CARBIDE (Hard Metal Disease)

Introduction

Tungsten, a greyish metal, is classified as a transition element and closely resembles molybdenum in its physical and chemical properties. Wolframite ((FeMn)WO₄) is the most important ore containing tungsten, while Scheelite (CaWO₄) is a principal domestic ore (45).

Currently, approximately 70% of the tungsten production in the United States is used in the manufacture of cemented tungsten carbide or "hard metal" (a mixture of tungsten carbide, cobalt, and/or other metals and their oxides or carbides) to form a material with a hardness nearly equal to diamonds (7)(43). It is used as an abrasive or briquetted with cobalt or other binders into tools for high-speed cutting of metals or hard materials. Tungsten compounds and cemented tungsten carbide are reported to cause both transient and chronic pulmonary disease.

Table II-30
OCCUPATIONS WITH POTENTIAL TUNGSTEN EXPOSURE

<ul style="list-style-type: none"> Alloy makers Carbonyl workers Ceramic workers Cemented tungsten carbide workers Cement makers Dye makers Dyers Flameproofers High-speed tool steelworkers Incandescent-lamp makers Industrial chemical synthesizers Inkmakers Lamp-filament makers Lubricant makers 	<ul style="list-style-type: none"> Melting, pouring, casting workers Metal sprayers Ore-refining and foundry workers Paint and pigment workers Paper makers Penpoint makers Petroleum refinery workers Photographic developers Spark-plug makers Textile dryers Tool grinders Tungsten and molybdenum miners Waterproofing makers Welders
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Source: (43)

List of Causative Agents (Manufacturing Processes)

The major compounds of tungsten to which workers are exposed are ammonium-P-tungstate, oxides of tungsten (WO_3 , WO_3 , WO_2), metallic tungsten, and tungsten carbide (43).

Tungsten carbide is produced by blending and heating tungsten and carbon in an electric furnace, and then mixing in a ball mill with cobalt to form a matrix for tungsten carbide crystals and other metals such as chromium, nickel, and titanium. Tantalum may be added depending on the properties required (28). All constituents are present in a finely divided state with a mean diameter reported to be about 1.5μ (10). The powdered metal is then pressed into ingots and fused. All processes of drying, grinding and drilling, finishing, and cleaning equipment are dusty (28). In the production and use of tungsten carbide, exposure to the cobalt or nickel used as a binder or cementing substance may be an important hazard to workers (29)(42).

Tungsten carbide usually constitutes 80% or more of the hard metal; the content of cobalt is usually less than 10%, but may be as high as 25% (43). When the cobalt content is greater than 2%, there is a potential cobalt health hazard, perhaps exceeding that of tungsten carbide; a nickel content greater than 0.3% represents a significant health hazard risk from nickel (43). In addition, the tungsten carbide industry uses other metals such as tantalum, titanium, niobium, chromium, and vanadium during the manufacturing process which also represent potential health risks.

List of Occupations and Industries Involved
See Table 11-30, page 438.

Epidemiology

Diffused pulmonary fibrosis (2)(3)(6)(10)(12)(15)(20)(24)(26)(38)(44) and bronchial asthma (5)(6)(9)(10)(14)(17) have been reported following either short-term or long-term occupational exposure to tungsten and its compounds in the cemented tungsten carbide industry. Changes have been reported for individuals exposed only to tungsten carbide (10)(14)(20)(26). It has been estimated that perhaps 9-11% of hard metal workers exposed to tungsten carbide develop pulmonary fibrosis (20)(26). While animal studies document the specific pulmonary toxic effect of tungsten and some of its compounds

(8)(13)(26)(27)(34), most reports of occupational exposure concern the effects of mixed dusts which contain not only tungsten carbide but also cobalt and other materials (4)(5)(6)(9)(10)(14)(15)(19)(32)(38)(39). Concentrations of tungsten are reported in only a few cases (28). Dust particles that are generated in operations where tungsten is processed are largely respirable, the majority being less than 5μ in diameter (6)(14)(16)(26)(30).

Estimated Population at Risk

NIOSH estimates that there are at least 30,000 employees in the U.S. who are potentially exposed to tungsten and its compounds (43). These figures are based on actual observations reported in the National Occupational Health Survey (NOHS). There are perhaps 15,000 to 20,000 persons potentially exposed to dusts in the hard-metal industry throughout the world (28). Only a small portion of exposed persons appear to develop respiratory disease (10). It has been estimated the 9-11% of hard metal workers exposed to tungsten carbide develop pulmonary fibrosis (20)(26). However, in one industry, only 9 of 1,500 workers were reported to have pulmonary disease (10).

Pathology

There are two major types of pulmonary reactions that occur among workers exposed to tungsten carbide: an asthma syndrome and diffuse interstitial pulmonary fibrosis. The interstitial fibrosis does not appear to differ from interstitial fibrosis produced by other agents (10). On microscopic examination, the lung shows an interstitial cellular infiltration and variable fibrosis. There are dilated alveolar spaces, lined by epithelium showing metaplastic changes. In some areas there are accumulations of what appear to be Type 2 alveolar pneumocytes and alveolar macrophages within alveoli lumen. Large mononuclear and even occasional multinucleated giant cells may be present. Electron microscopic changes are consistent with those observed by light microscopy (10). X-ray diffraction analysis shows the presence of tungsten carbide and mass spectrometric analyses document the presence of tungsten carbide and cobalt in lung tissue (10). In the study of 12 cases of diffuse pulmonary fibrosis reported by Coates and Watson, a lung biopsy sample contained 2.0 mg of tungsten, 2.0 titanium, and 0.1 μ g of cobalt/

gm of wet lung (10). There was no correlation between cobalt content of lung tissue and severity of disease. In another study by Coates et al., light and electron microscopic examination were performed on specimens from a case of diffuse interstitial fibrosis, a second with subacute interstitial pneumonitis, and a third asymptomatic worker with clinically normal lungs (11). There were deposits of collagen and elastic tissue in alveolar areas associated with multifaceted crystals which appeared to cause tears in cells; the crystals were believed to be tungsten carbide. Finer, needle-like crystals were noted lying in macrophage lysosomes. There were alterations of alveoli Type I pneumocytes, with swelling and formation of microvilli. There were also occasional alterations of the capillary endothelial cells. In the asymptomatic individual, no abnormalities were noted in the alveoli or endothelial cells.

Beck reported the results of 12 workers with hard metal disease, 8 of whom died because of pulmonary disease (6). In general, there were varying degrees of interstitial fibrosis present. No correlation was noted between the duration of exposure and development of interstitial fibrosis. Baudouin reported electron microscopy of biopsied lung tissue in a man who worked in a hard metal factory (4). Crystalline particles, possibly tungsten carbide, were noted in alveolar macrophages. Examination of lung tissue by x-ray fluorescence demonstrated large amounts of tungsten, greater than usual amounts of titanium, and small amounts of tantalum and niobium. X-ray diffraction studies documented the presence of tungsten carbide and titanium carbide. The number of airspaces was decreased because of excessive mucus production and hyperplasia of alveolar epithelial lining cells. Alveolar macrophages containing foreign material were present. Spectroscopic and histochemical analysis of biopsy specimen material reported by Scherer indicated the presence of 2-10 times the normal amount of tungsten, but no cobalt was found (38). On the other hand, lung tissue analysis from a 46-year-old woman who worked with hard metal mixtures and was exposed to tungsten carbide and cobalt revealed an emission spectrographic analysis of lung tissue which showed no detectable levels of tungsten, titanium, or cobalt—possibly because of the small sample size (32). There was significant x-ray and pulmonary func-

tion test improvement when she left work; this worsened when she resumed her job.

Rats exposed to metallic tungsten by intratracheal injection or inhalation, showed a mild interstitial and perivascular inflammatory cell response (26). Increased collagen tissue was noted by eight months. Although tungsten itself caused mild interstitial fibrosis in rats, no significant response was noted following intratracheal injection of pure tungsten carbide (27). Because of this, it was speculated that the pulmonary fibrosis described in the hard metal industry was caused not by the tungsten carbide, but by coexisting exposure to cobalt. Delanhant's studies support this; tungsten carbide produced little effect on guinea pig lungs (13). Experiments were undertaken to determine which of the metallic components in cemented tungsten might provoke lung lesions. Tungsten metal, tungsten carbide, and carbon dust produced relatively little tissue response. Mixtures of tungsten carbide and carbon were more harmful to guinea pig lung tissue than tungsten metal alone (13)(33)(36). Particulate tungsten metal and a mixture of tungsten carbide and carbon appeared to be relatively inert, but when cobalt was mixed with tungsten carbide, an acute hemorrhagic pneumonia developed; this response seemed to characterize the cobalt component (33). A mixture of tungsten carbide and cobalt produced pulmonary fibrosis in guinea pigs, especially in areas where there was dust deposition (37). Even one year after injection, dust particles remained within alveolar spaces together with residual pneumonitis, mild cellular reaction, and fibrotic reaction around the dust deposits.

Schepers theorized that the marked proliferative and metaplastic epithelial changes noted could reflect a synthesizing property of cobalt (37). While changes in lungs following various mixed dusts exposures are similar, they are most marked when cobalt is one of the constituents. This suggests the activity of cobalt is enhanced when tungsten and cobalt combine (21). This may be due to the solubility of cobalt which is increased in the presence of tungsten (21).

Magnesium tungstate was very reactive in producing pulmonary lesions (34) whereas tungsten silicide caused hyperplastic lymph nodes, focal thickening of alveoli walls, perivascular lymphocyte infiltration, and nodular accumulations of fibroblasts, lymphocytes, and macrophages (8).

cytes, and macrophages (8). Rats exposed to tungsten hexachloride inhalation died of pulmonary edema (40). Interstitial pulmonary inflammatory responses occurred after administration of calcium-magnesium-tungstate phosphor in rats; the most accentuate lesions appeared in areas of dust accumulation (16). Animal studies comparing tungstic oxide, sodium tungstate, and ammonium-p-tungstate demonstrated greater mortality rates in animals as the tungsten content of their diet was increased, especially when it was greater than 2% (22).

While total dust levels and cobalt concentrations are reported in many studies, actual tungsten concentrations are documented in only a few cases. The size of the dust particles generated during various operations in which tungsten is processed and used is generally less than 5 μ in diameter (6)(14)(16)(26)(30).

Clinical Description

There are two major types of respiratory disease seen among tungsten carbide workers: reversible, rather acute airways obstructive syndrome (asthma) and diffuse interstitial fibrosis.

The acute asthmatic syndrome is characterized by productive cough and chest tightness which usually develops towards the end of the workday or in the evening (9)(10)(14). Symptoms improve during weekends and vacations but again recur within the first few days after returning to work. The airways obstructive disease is reversible, showing improvement following administration of bronchodilators; it is eliminated by removal from exposure (9). Atopic and non-atopic individuals are affected equally (9).

Individuals with interstitial pulmonary fibrosis develop a rapid onset of cough, sputum, and dyspnea on exertion (28). On physical examination, basilar rales are heard. The chest x-ray is abnormal and characterized by linear or ill-defined irregular opacities; there is some prominence near the hilar area. Disease onset usually occurs within one or two years after beginning employment. In some cases, resolution of symptoms are noted following removal from work (4)(14)(25)(27)(35). Although lung biopsies obtained early in the course of the disease show a desquamative interstitial pneumonia, biopsies taken later reveal a more chronic disease, characterized by diffuse interstitial fibrosis (35). Fibrosis develops in some workers

within 2 years, but in others it may not develop until 25 years of employment; usually it occurs after 10 years of work (1)(6)(10)(18)(19)(25)(27)(31)(35). The clinical, physiologic, and x-ray features are similar to those of other types of diffuse interstitial fibroses. In a few cases, individuals have died with respiratory or cardiac failure. Opacities on chest x-ray do not appear more radiodense even though the atomic number of tungsten is 74. Increased gamma globulinemia has been reported in some affected individuals (27).

Treatment with corticosteroids may be indicated, particularly in the desquamative interstitial phase (28).

Diagnostic Criteria

Diagnosis depends on obtaining the proper occupational history as well as demonstrating characteristic x-ray and pulmonary function abnormalities consistent with an interstitial fibrotic response. This is also true for the asthma syndrome.

Methods of Prevention

Because of the 9-10% incidence of pulmonary fibrosis, NIOSH has recommended that employees exposed to tungsten alone, without cobalt exposure, have a recommended 10-hour shift (40-hour week) Threshold Limit Value of 1 mg/m³, measured as tungsten. Because the major industrial exposure in the cemented tungsten industry occurs along with exposure to cobalt with mixture percentages ranging from 3-25%, NIOSH has recommended that employees exposed to cemented tungsten carbide which contains more than 2% cobalt have limited exposure. Exposure should be similar to the current standard for cobalt which is 0.1 mg/m³ measured as a time-weighted-average concentration. When tungsten carbide is made with nickel as a binder rather than cobalt and the nickel content exceeds 0.3%, NIOSH has recommended that the TLV for nickel of 15 μ g/m³ should apply (43).

Medical surveillance should include a pre-placement evaluation consisting of a medical and physical examination, chest x-ray and pulmonary function tests, as well as periodic examinations with similar laboratory and medical studies. Engineering controls, such as enclosures and local exhaust ventilation, should be used to keep the concentrations of airborne dust at or

below the appropriate time-weighted average exposure limits. Respiratory protective equipment should not be used in place of engineering and ventilatory controls. Care should be taken by employees when pouring or scooping powdered material in order to avoid excessive dust generation (43).

Research Needs

Epidemiology studies are needed to better assess the long-term effect of tungsten exposure by itself. Studies are necessary to determine whether there are synergistic or potentiating effects from other metals (e.g., cobalt and nickel) and compounds commonly found with the tungsten compounds used.

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FIBROUS GLASS AND OTHER MAN-MADE MINERAL FIBERS

Introduction

Man-made mineral fibers are those made from glass, natural rock or any readily fusible slag. They differ from naturally occurring fibers, such as asbestos, which are crystalline in structure and differ chemically (27). Glass fibers are composed of either borosilicate or calcio-alumina silicate glass. They contain no trace elements of biological significance. A glass fiber refers to any glass particle with a length to diameter ratio of at least three to one. The health effects of man-made mineral fibers may be different depending on the length and diameter of individual fibers.

List of Causative Agents (Manufacturing Processes)

Slag wools, rock wools, and glass wools and filaments are all glass-heated mineral fibers behaving in much the same manner but having important differences and individual properties. Some of the important differences relate to structure, frequency of occurrence, and chemical resistance—particularly solubility.

Mineral wool, originally obtained as a natural product of volcanic craters in Hawaii, usually consists of fine, pliant, vitreous fibers which are incombustible and nonconductors of heat. Rock wool, made by blowing molten rock, is more uniform than mineral wool and has physical characteristics which depend on the class of rock used. For instance, rock wool made from high-silica limestone is used for insulating oven walls requiring temperatures up to 1,000°F.

Man-made mineral fibers can be manufactured to various diameters and fall into three broad category groups: (1) Continuous filament, which is used in textiles and as a reinforcement in plastics and other materials. The filaments are of relatively large diameter, perhaps 9-25 μ in size. Production methods give a narrow variation of diameter size around a normal size. (2) Insulation wool is usually about 6 μ in diameter and has a much wider distribution around a nominal diameter. A high proportion of fibers may have diameters less than 3 μ which can be used for

special application such as acoustic insulation. (3) Small (and sometimes uncoated) fibers below 1 μ in diameter are produced for a limited, specialized market—representing only about 1% of all production. Continuous filament and special purpose submicron range fibers are made exclusively from glass, whereas insulation wools can be manufactured from rock or slag (27).

Mineral fibers are glassy cylinders and, therefore, can never split longitudinally; they only break across. As they are destroyed, they form fragments which no longer have the character of fibers. The structure of technically-used asbestos fiber is totally different; it is always present as bundles, never as a single fiber. Individual fibrils may be as small as 2-30 μ in diameter. Because of the size of individual asbestos fibers, a bundle of asbestos fibers of the same diameter as mineral fibers would contain about 785,000 fibers. Fibrous glass processes may be classified as "textile" or "wool" operations (41). Textile fibers, formed as continuous filaments, have diameters greater than 3.0 μ and have wide application in textile, fabrics, and reinforced plastics industries. Fibers produced by wool-forming methods may be as small as 0.5 μ in diameter and less than 1 μ in length (16) and are mainly used for thermal insulation. Fibrous glass structure has silicon dioxide (SiO_2) as a major network form, with boron and aluminum oxides also contributing as network formers. The three dimensional network and tetrahedral configuration of SiO_2 molecules provide important and unusual properties which can be varied and adjusted by addition of various modifying ingredients (14).

Wool-type fibrous glass provides effective insulation because fibers are formed into interlocking network masses which entrap air into many small cells and restrict flow of heat. Thus, the density and diameter of fibrous glass fibers influence insulation properties by affecting the size of air cells and the structure of the interlocking glass fiber blanket. Decreased thermal conductivity and better insulation result as fiber diameter decreases. However, the linear relationship between fiber diameter and thermal conductivity no longer occurs when fiber diameters are very small.

Other important properties of fibrous glass besides insulation properties include chemical resistance, high tensile strength, and acoustic

insulation.

Man-made mineral fibers are usually coated with a binder (mainly a thermosetting resin) such as urea-formaldehyde type which is fully polymerized in the finished product. Rock wool may be produced with only an oil as a lubricant and for special application. Some glass fibers are of very fine-diameter and produced without any coating at all. Surface treatments are performed in order to bind and protect fibers and to reduce the effects of impact and friction (35)(43)(47). This treatment may introduce occupational health problems (41).

Estimation of environmental exposure to fibrous glass may be made gravimetrically by determining the weight of dust-per-volume of air sampled or quantitatively by the number of actual fibers counted per volume of air sampled. In general, gravimetric analyses provide an indicator of fibrous glass exposure to larger diameter fibers, i.e., greater than 3.5 μ . It does not accurately measure exposure to small diameter fibers. The relationship between fiber number and fiber weight varies considerably with fiber dimensions (16). The weight of fibrous glass dust is independent of the numbers of small fibers present and is more a function of the square of fiber diameter. A disproportionately greater number of very large-diameter fibers can increase the weight of the fibrous glass dust sample appreciably, and if large fibers constitute a small part of the dust, then a marked disagreement between gravimetric and fiber count may occur. Therefore, counting fiber numbers provides a more accurate estimate of exposure to small diameter fibers, i.e., less than 3.5 μ .

NIOSH has recommended fiber count for estimating numbers of small diameter fibers present and gravimetric analysis for determining large diameter-size fibers (52).

In the majority of occupational exposures to fibrous glass, there are fibers of varying diameters present, including a substantial percentage of fibers of respirable size. A number of industrial hygiene surveys have related different occupational and environmental sources of fibrous glass (1)(4)(11)(13)(16)(20)(28)(29). In most facilities using or producing fibrous glass with diameter size more than 3.5 μ , fiber counts of less than 1,000,000 fibers/ M^3 (or one fiber/cc), and gravimetric measurements of less than 2.0 mg/ m^3 (1-5 mg/ m^3) have been noted (1)(11)(13)(16)(20)(29)(31)(50). In operations where fiber

diameters are less than 3.5 μ , higher mean fiber counts are noted, ranging between 1,000,000 and 21,000,000 fibers/ m^3 , with an average of 3,000,000 fibers/ m^3 (16)(20)(28)(31).

List of Occupations and Industries Involved

There are normally small amounts of fibrous glass present in urban air, reflecting its presence in our society (3). Concentrations range between less than 1,000 and up to 10,000 fibers/ m^3 of air with levels of 30-130 fibers/ m^3 being found even in remote rural areas. While fibrous glass used in ventilation ducts potentially represents a source of glass fibers in the air of buildings (7), the air concentrations of such fibers is extremely low, averaging about 1,000 fibers/ m^3 of air (2)(12).

The major use for fibrous glass products is in thermal and acoustical insulation, and as reinforcement for various processes especially in the plastics industry (i.e., boats, shower stalls, etc.). Building insulation used in homes is installed between roof rafters and studs of sidewalls. A flexible fibrous glass blanket provides a lining for refrigerators, stoves, furnaces, and hot water heaters. A molded type insulation is used for automobile hoods, car bodies, refrigerator ships, acoustic and thermal insulation, and also for decorative purposes. Rigid board-type material may provide ceiling board and roof insulation for factory or warehouse decks. Fibrous glass-pipe insulation controls heat on steam lines and is used for temperature control and coal applications in chemical processing plants, utility plants, and commercial and mechanical applications (5). A semi-rigid type of fibrous glass boards is used in chemical processing tanks as low velocity air transmission systems for ducts and for metal building insulation such as on the roofs of prefabricated buildings.

Dust and fumes are produced when fibrous glass products are trimmed, chopped, cut or sawed, or during oven curing of the binder systems. Dust is not a problem during the basic fiber wool forming process. Packing processes with application of mechanical pressure to reduce product volume are often dusty. In industries utilizing wool-type fibers, dust is generated when producing loose fibers, or from pouring and blowing wools (31). Airborne fiber counts are reported to be low for textile-type fibers as they are processed into finished products during spinning, weaving, twisting, plying, and chopping opera-

tions (21). High dust levels are noted in operations involving insulation. Fibrous glass dust exposure occurs when rolled fabrics are cut to various shapes, during spraying when fibers are chopped simultaneously with application of catalyst resins, and during finishing operations when material is removed and imperfections are ground.

Epidemiology

The majority of human cross-sectional prevalence studies have reported no significant pulmonary effects from fibrosis (17)(22)(28)(38)(54)(57). Studies utilized pulmonary function tests and chest x-rays. Workers were employed up to 30 years and, in most cases, exposure was to fibers having a diameter of about $6\ \mu$ with fiber concentrations averaging about $70,000\ \text{fibers}/\text{m}^3$ (11)(57). Only a few human studies are available to suggest chronic health effects occur from fibrous glass exposure; these studies mainly report an excess mortality from nonmalignant respiratory disease (19). However, in a 1977 report prepared for the medical and scientific committee on the Thermal Insulation Manufacturers Association, Enterline and Marsh presented preliminary information on a mortality study of 5,443 fibrous glass workers from five plants and 955 mineral wool workers from three plants, who had worked at least one year during the period January 1, 1945, through December 31, 1963 (19). No excess mortality risks were observed for malignant or nonmalignant respiratory disease, nor were excess lung cancer deaths observed in two plants which manufactured small diameter ($1\text{--}3\ \mu$) fibers. There was no association between intensity of exposure and death from malignant and nonmalignant lung diseases. The investigators stressed the preliminary nature of their findings and withheld final conclusions until all data was analyzed.

Carcinogenic responses in animals, particularly rodents, following intrapleural or intraperitoneal fibrous glass administration is similar to the responses found after implantation of any foreign material such as polyethylene, asbestos, nylon, cellophane, or teflon (10)(15)(40)(46)(55). Tumor development in laboratory animals following pleural or intraperitoneal administration of fibrous glass material probably represents a non-specific foreign body response. The response depends on the physical characteristics of the fibrous glass, the most important being size and

shape; certain characteristics of the animal; and the length of time the fibrous glass is present in the animal (a critical factor). On the basis of present information, fibrous glass cannot be considered a carcinogenic agent.

NIOSH has recommended that occupational exposure to fibrous glass having diameters equal to or less than $3.5\ \mu$ (53) and lengths more than $10\ \mu$ be limited to a 10-hour time-weighted-average concentration of $3,000,000\ \text{fibers}/\text{m}^3$. This should especially protect workers in operations using small diameter fibers. NIOSH also recommends limiting dust exposures (measured gravimetrically) to $5\ \text{mg}/\text{m}^3$ so as to also reduce exposure to larger diameter fibers. The recommendations are designed to control exposure to both small diameter fibers, which might have potential long-term adverse health effects, and larger diameter fibers, which can cause skin, eye, and respiratory tract irritation (18)(25)(26)(33) and possibly increased mortality due to non-malignant respiratory disease (6)(19). Most fiberglass irritation effects can be minimized when proper work practices are followed. Workers having dermographism and atopic dermatitis probably should not work with fibrous glass (39). Periodic examinations of workers—including pulmonary function testing and chest x-rays—seem necessary because of potential respiratory disease as a result of fiberglass exposure (6)(19)(30)(36)(37).

When workers are exposed to fibers less than $3.5\ \mu$ in diameter, a lung cancer screening program seems reasonable. Respiratory protection becomes necessary only when large amounts of dust are generated, and where environmental exposure cannot be adequately handled by engineering controls. Good personal hygiene by workers is important in order to avoid or minimize skin problems. There should be washing facilities and showers available at work before workers change into street clothes and employers should provide laundered work clothes. Gloves or other types of protective clothing may be helpful in reducing direct contact with fibrous glass and subsequent skin problems. Good house-keeping practices are extremely important in minimizing exposure (42)(43). Vacuuming, cleaning, washdown procedures, and wet sweeping can be helpful in reducing dust concentrations. On the other hand, dry sweeping or blow-down with compressed air generates dust and should be

discouraged. Scrap material and debris should not be allowed to accumulate; waste material should be disposed of properly. Finally, concern for other potentially hazardous substances such as resins, solvents, and pesticides used with fibrous glass is also necessary.

Estimate of Population at Risk

According to NIOSH about 200,000 workers in the United States are exposed to fibrous glass in the manufacturing of about 20,000 products (53). The amount of fibrous glass insulation has increased since the government required that 36,000,000 homes meet Federal insulation standards by 1963 (53). Approximately 3,000 workers are exposed to mineral wool.

Pathology

The behavior of a glass fiber in air is mainly determined by its diameter and less by its length.

Timbrell reported that fibers with aerodynamic diameters larger than 3.5μ were primarily deposited in the nasopharynx, trachea, and bronchil; fibers with diameters less than 3.5μ penetrated into the alveoli; maximal alveolar deposition occurred with fibers of 2μ diameter and decreased to a minimum deposition of about 20% with fibers 0.4μ in diameter (52). Mathematical models estimate approximately 30% of fibers 25μ long and with a proper diameter could be deposited in the alveoli (23)(24); perhaps 1-3% of the fibers could be deposited in alveoli when fiber length increased up to 200μ .

A number of animal studies have been performed exposing animals to fibrous glass by various routes (21)(32)(34)(48)(49)(55)(56). In studies addressing the fibrogenic potential of fibrous glass, length and diameter are important factors (21)(32)(43)(56). Fibers having a length greater than 10μ are more likely to produce pulmonary fibrosis in animals; fibers shorter than 5μ generally do not. Kuschner and Wright studied the effects of glass fibers of different dimensions (32). Groups of 30 guinea pigs were intratracheally injected with one of six possible categories of glass fibers differentiated according to dimensions. No fibrosis was found after exposure to short fibers. Exposure to long fibers (greater than 10μ) resulted in an interstitial reaction around respiratory bronchioles and proximal alveoli. Thin (less than 1μ) and long fibers caused a fibrotic reaction whereas thin and short

fibers did not. Short and thick fibers caused some interstitial fibrosis after two years. Long and thick fibers caused focal areas of interstitial fibrosis.

There have been a number of pathologic studies of human lungs reported (8)(9)(22)(41)(47). Postmortem studies performed on lungs of 20 workers who had been exposed to various concentrations of fibrous glass for 16-32 years were compared with the lungs of 26 urban dwellers of both sexes who presumably had not been occupationally exposed to fibrous glass dust (22). Quantitative analyses of lung tissue of fibrous glass workers demonstrated total dust levels of about 2% (range, 0.8-4.2%); actual fiber content was approximately 95,000 fibers per gram of dry lung (range, 20,000-200,000). These fiber counts were no different from fiber counts noted in the lungs of controls. There was no correlation between lung fiber count and duration of severity of occupational exposure. The highest percentage of fibers grouped according to length were between 16μ and 25μ , with 90% of the fibers having diameters less than or equal to 3μ . No specific tissue change was identified in the lungs of fibrous glass-exposed workers who became ill following a heavy exposure to fibrous dust from the insulation of an old hot water heater (37). Examination of lung tissue obtained following a right lower lobectomy revealed multifocal abscesses containing minute fiberglass particles, similar to the particulate matter obtained from the actual insulating material. Adverse health effects reported from large diameter fibers have included mainly skin, eye, and upper respiratory tract irritation (18)(25)(26)(33). There are no indications that fibrous glass acts like asbestos in humans except possibly where there are high concentrations of submicron fibers. This condition occurs rarely, if ever, and is not expected to occur significantly in the future. Larger diameter fibers have different biological characteristics than smaller diameter fibers (32); fibers with a diameter of 3.5μ and smaller penetrate into alveoli (13)(16)(22)(31)(51)(52). Fibers of longer length, i.e., 10μ or greater, appear to be more biologically active than shorter length fibers. Health effects reported to occur with exposure to small diameter fiberglass are rare and generally confined to skin and respiratory tract irritation. Small diameter fiberglass is a relatively new material and population exposures for long

periods of time have not yet occurred. Chronic effects similar to those observed with asbestos have not been noted in individuals occupationally exposed to fibrous glass. Although fibrous glass was first manufactured in the 1930's, its extensive use did not occur until the 1940's and 1950's. Fibers having diameters less than 3.5μ did not have large-scale use until the 1960's (41)(47). Therefore, chronic health hazards from small diameter fibers may not be appreciated since sufficient exposure in terms of numbers of people exposed and duration of exposure may not have occurred, nor has enough time lapsed for potential chronic effects to be recognized. There has been concern that occupational exposure to fibrous glass having fiber dimensions similar to those of asbestos might lead to similar chronic effects. There are a number of factors which might mitigate against this, including the presence of fewer numbers of small diameter fibers in fibrous glass workplaces than usually existed in asbestos operations (53).

Unlike asbestos, fibrous glass does not fracture linearly to produce small diameter fibrils. Furthermore, fibrous glass is less durable than asbestos and is more easily fragmented and rapidly cleared from the lungs (8)(9).

Clinical Description

There are no specific clinical, x-ray, or pulmonary function test changes that are reported to be characteristic of fibrous glass exposure. Surveillance should be conducted because of the potential chronic health effects.

Diagnostic Criteria

No special diagnostic test is appropriate.

Research Needs

More information is needed on the health effects of fibrous glass of small diameter size, particularly since glass fibers less than 3.5μ diameter are relatively new in industry. Especially needed are studies of very small diameter fibers i.e., less than 1μ . There are still a number of unanswered questions concerning health effects of fibers with diameters larger than 3.5μ . Studies are necessary to determine the chronic long-term effects of inhalation of fibers of various dimensions and to identify potential mechanisms of fibrogenesis and possible carcinogenesis. More industrial hygiene data is needed to characterize the extent of exposure to fibers with diameters

less than 3.5μ . Improvement in analytical methods for fibrous glass is necessary in order to determine precision and accuracy. The importance of physical features of fibers needs to be explored such as fibers splitting, role of fiber fragmentations, and importance of fiber solubility in relation to tissue effects.

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ZIRCONIUM

Introduction

Zirconium is a silvery-white metal, more abundant than nickel, but difficult to reduce to metallic form since it combines so readily with oxygen, nitrogen, carbon, and silicon (1). Animal experiments have indicated that zirconium compounds are capable of causing both pulmonary granulomas and interstitial fibrosis (2)(10). There are no well-documented similar effects in humans.

List of Causative Agents (Manufacturing Processes)

Zircon ($ZrSiO_4$) and baddalyte (ZrO_2), the most common naturally occurring forms of zirconium, are derived from igneous and sedimentary rock and recovered commercially from beach sands and river gravel (9). Zirconium occurs mixed in the form of platelets, flakes, or bluish-black amorphous powder but is never found in a free state. While it is generally regarded as a rare metal, it is present in the earth's crust in amounts larger than lead, copper, or zinc, with concentrations about 0.22% (15).

Zirconium may be prepared by chlorination—either of zircon or of a carbide made from it by heating with carbon (3). This mixed tetrachloride of zircon and silicon are then separated and the crude zircon tetrachloride is

further purified by sublimation in hydrogen gas. This is further reduced in vapor from magnesium or sodium, the residual zirconium being in the form of a sponge which is highly reactive and must be conditioned before being exposed to the atmosphere. A second method of preparation is by thermal dissociation of the zirconium tetraiodide on contact with a hot filament at a temperature of approximately 1,300°C (3).

Pure zirconium has important properties, especially that of high resistance to corrosion by alkalis and most acids (4). It is very reactive, especially in the moist powder form and is likely to cause an explosion. This is an onerous problem since the ignition temperature of zirconium is low (20°C) and it can readily be ignited by sparks or small flames. Zirconium fires should not be extinguished by water because this may cause a violent explosion (7).

List of Occupations and Industries Involved

Zirconium oxide (ZrO_2) is a fine crystalline powder which is used for fused or sintered ceramics and for crucibles and furnace bricks (1). Zirconia bricks have been used for lining electric furnaces. Zirconia foam is marketed in bricks and various shapes are used for thermal insulation (1). Stabilized zirconia has a low coefficient of expansion and white-hot parts can be plunged into cold water without breaking. Zircon crystals are valued as gemstones since the high refractive index gives it a great brilliance. Zirconia fibers are used for high temperature textiles and are produced from zirconia with about 5% lime for stabilization. Zirconia fabrics are woven, knitted, or felted of short-length fibers and are flexible.

Zirconium powder is very reactive and is used for making sintered metals or making sintered parts. Alloys are frequently produced including zirconium copper, nickel, or cobalt. Zirconium alloys with high zirconium content have atomic applications. Small amounts of zirconium are used in many steels, zirconium being a powerful deoxidizer which removes nitrogen and combines with sulfur. It reduces hot-shortness and gives steel ductility (1). Zirconium carbide (ZrC_2) is produced by heating zirconia with carbon at about 2,000°C. The crystalline powder is used as an abrasive and for hot-pressing in heat resistant and abrasion-resistant parts. Zirconium ceramics are valued for electrical and high-temperature parts and refractory coatings.

Zirconium has industrial uses: for nuclear reactors; as a shielding material in high vacuum tubes and radio valves, chiefly because of its affinity for various gases; in steel manufacture as an alloy with silicon and manganese; as a constituent of alloys such as nickel and cobalt in order to increase wear resistance, or with niobium and tantalum in the manufacture of non-corrosive chemical apparatus; as a substitute for platinum; in cast iron manufacture; as a refractory lining for electric furnaces; as an igniter for photoflash bulbs; as an alloy with lead for lighter flints; as a substitute for mercury fulminate for detonators; in a concentrated arch lamp which gives the nearest approach to a point source; in the ceramic and glass industries as an opacifier and a polishing powder for lenses in television tubes; as pigments in plastics; and as a catalyst in organic reactions (3). Zirconium is utilized as a foundry sand and abrasive; as a refractory in combination with zirconia; as a coating for casting mold; a catalyst in alkyl and alkenyl hydrocarbon manufactures; as a stabilizer in silicone rubbers; and as a gem stone. In ceramics it functions as an opacifier for glazes and enamels and it is used in unfrittered glass filters. Zirconia itself is used in die extrusion of metals and in spout linings for pouring metals as a substitute for lime in oxyhydrogen light (16). It is also used as a pigment, in metal cutting tools, thermocouple jackets, waterproofing textiles, and treating dermatitis and poison ivy.

A list of occupations in which exposure to zirconium may occur includes (16):

- abrasive makers
- ceramic workers
- crucible makers
- deodorant makers
- enamel makers
- explosive workers
- foundry workers
- incandescent lamp makers
- pigment makers
- refractory material makers
- vacuum tube makers
- glass makers
- metallurgy
- raylon spinneret makers
- textile waterproofers

Epidemiology

There have been no detailed epidemiologic studies.

Population at Risk

It has been estimated by NIOSH that there are approximately 1.3 million employees exposed to zirconium compounds, especially zirconium oxide (17).

Pathology

Early animal studies indicate that zirconium is inert and does not produce any significant pulmonary pathology (5)(6). Suspension of finely ground zirconium, when injected intravenously, intraperitoneally, or intratracheally, is without apparent effects and no significant pathological changes have been noted (5). When rats were exposed to very high concentrations of zircon dust daily for several months and then killed, dense radiologic shadows were noted on radiographed sections (6). These shadows were produced by aggregations of phagocytes containing zircon particles. There was also a slight inflammatory response, but essentially no significant lung reaction. Animal exposure studies with zirconium metal were generally negative (11). Skin granulomas from deodorant sticks containing zirconium salts have been described (12)(13)(14)(18). A typical zirconium deodorant stick is a gel containing sodium stearate, ethyl alcohol, carbopol, and water with about 10% of an aqueous 45% solution of sodium zirconium lactate (approximately 0.5%) (3). The skin granulomas were described as reddish-brown papules being 1-4 mm in diameter. Biopsied lesions did not reveal zirconium in the granulomas even with examination by x-ray fluorescence and emission spectrometry (3). The skin eruptions were described after several months of use. They generally disappeared spontaneously but slowly, sometimes persisting for months or years (14) (15). These skin reactions were believed to be due to a hypersensitivity to zirconium (14)(15).

There are no reports available of good pathological studies on human lung. Peribronchial granulomas have been produced in rabbits following inhalation of sodium zirconium lactate (10). Diffuse pulmonary fibrosis has been reported to occur in a variety of experimental animals after prolonged inhalation of zirconium lactate (2). Reed reported a case of a pulmonary

granulomatous reaction in a chemical engineer associated with the process of a purification and reduction of zirconium metal (11). Twenty-two workers who had been exposed to the fumes of this process for 1-5 years were also evaluated (11). None of these workers showed granulomatosis and 15 had no pulmonary symptoms; 5 had symptoms of chronic bronchitis, 3 of whom were also exposed to chlorine gas. The original case, which was believed to have zirconium-induced disease, was subsequently found to have chronic beryllium disease and had been exposed to beryllium seven years previously.

Clinical Description

There appear to be no clinical effects of zirconium and zirconium compounds in man. There are no lung function studies on record.

No x-ray changes attributable to zirconium were reported by Reed in 22 workers exposed for a period of 1-5 years in a zirconium plant (11). McCallum reported the presence of small densities (Categories 1-3) on chest x-rays of eight men working in a zirconium process plant adjacent to an antimony smelting plant (8). The significance of the x-ray changes is not known.

Diagnostic Criteria

Since zirconium is widely used in industry, it is possible that a pneumoconiosis could be caused by zirconium dust. Perhaps the occasional report of small opacities seen on chest x-ray in molders and knockout foundry men using molding sand and parting powders containing zircon are caused by zirconium rather than iron. One must be cognizant, therefore, in light of changes noted in animals, of the possibility that zirconium compounds may cause chest x-ray opacities and perhaps diffuse granulomatous pneumonitis and interstitial fibrosis (9):

Methods of Prevention

Dust concentrations should be kept to a minimum. Good general housekeeping and safety practices are in order, as they are for any occupational exposure.

Research Needs

More studies are needed to determine whether zirconium compounds are capable of producing significant pulmonary disease in exposed individuals.

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RARE EARTHS

Introduction

The term rare earths usually refers to the lanthanum (or lanthanons) series of metals having atomic number 57-71, and includes yttrium with atomic number 39 (11). They are part of the transition metals Group 3, being the first series of the periodic tables and having similar molecular structures. They are found together in various combinations in many ores: the most important are monazite and bastnaesite, but also xenotime, gadolinite, samarskite, fergusonite, apatite, and euxenite. Cerium, atomic number 58, is the most abundant rare-earth metal, but thorium oxide is also present in small amounts in monazite and yttrium. Norway, Sweden, the United States (Idaho, California and South Carolina), Ontario, Canada, and Brazil are the principal suppliers of rare earths. In the series with atomic number 57-71, each metal has 2 outer electrons and 8 or 9 electrons in the next inner shell. The metals vary in their third shell from the outside, with each element above lanthanum having one electron more in the third layer than the element below it (57). This makes the mass and atomic weight larger, but the additions of these electrons make little difference in the physical properties of the metals (11). Con-

sequently the rare earths are very similar and separation of them is difficult (12).

List of Causative Agents (Manufacturing Processes)

The rare-earth metals are usually found together in ore. The metals with atomic number 57-63 and including cerium (58) have also been referred to as light rare earths (3). Yttrium (atomic number 70) is also included in this group because of its light weight.

When thorium is separated from monazite ore, the residual matter may be reduced by electrolysis to an alloy which contains about 50% cerium together with other rare metals (3), and is called misch metal, a German name for mixed metal. Misch metal is used for making aluminum alloys and some steels and iron. It is useful in removing sulfur and oxides and completely degassifies steel. It is used as a precipitation and hardening agent for stainless steel. Another important use of misch metal is in the manufacturing of magnesium for aircraft castings.

Cerium oxide, a pale yellow, heavy powder, is used for coloring ceramics, for producing distortion-free optical glass and for decolorizing crystal glass. Cerous oxide (Ce_2O_3) makes glass completely absorbent to ultraviolet rays and is thus an excellent opacifier for ceramics. Neodymium is used in magnesium alloys to increase strength and elevate temperatures and is used in some glasses to reduce glare (3). Lanthanum oxide, a white powder, is used for absorbing gas in vacuum tubes; the bromine is used as an electron admitter for maintaining a constant active cathode surface and has a high electric conductivity.

Didymium is not an element but a mixture of rare earth without cerium. It contains the oxides of lanthanum, neodymium, praseodymium, samarium, and other oxides. It is really the basic material in which the rare metals are produced. It gives glass a neutral grey color and is used in glass for welders' goggles because it absorbs yellow light and reduces glare and eye fatigue.

Dysprosium has high corrosion resistance and has good neutron-absorption ability. It is used in nuclear reactor control rods, in magnetic alloys, and in ferrites for microwave use. It is also used in mercury arc lamps.

Cerium is used in coloring glass yellow, but can also be used to enhance the clarity of white glass (11). It gives a blue fluorescent quality to

glass when made in reducing conditions, but if made in an oxidizing process, it produces no fluorescence. It is also used to prevent color changes in glass when exposed to ultraviolet. Cerium has replaced rouge in polishing glass. It is also used as a dye in the textile industry for mildew-proofing. Cerium constitutes about 50% of the makeup of misch metal used in magnesium and ferrous alloys.

Praseodymium is used to color glass, to make carbon arc cores for light and theater projection machines, search lights, and other intense lighting sources.

Neodymium is used to make purple glass and also used for stopping glass lasers.

Promethium is an important radioactive source and is used for luminescent dials.

Samarium is used in making infrared-absorbing glass and is a constituent of nuclear reactors.

Gasolinium has a high neutron absorption factor and is used in control rods and reactors. As an alloy, it improves high temperature characteristics of iron and chromium.

Metallic thorium is used in nuclear reactors to produce nuclear fuel, in the manufacture of incandescent lamps, and as an alloying material (18).

List of Occupations and Industries Involved

A partial list of occupations in which exposure to rare earths may occur includes:

- ceramic workers
- incandescent lamp workers
- metal refiners
- organic chemical synthesizers
- aircraft castings maker
- gas mantle workers
- alloy metal workers
- nuclear reactor workers
- neodymium tube makers
- glass (vitreous) makers
- rocket fuel makers
- light flint makers
- textile workers
- ink makers
- phosphor makers
- metal refiners
- enamel makers
- workers exposed to carbon arc lamps

Epidemiology

There have been essentially no significant epidemiologic studies of individuals exposed to rare earths. A few case reports are described in the section on Clinical Description.

Estimate of Population at Risk

The overall population at risk is unknown. NIOSH estimates that there are about 7,000 workers potentially exposed to cerium oxide.

Pathology

No pathological studies of human lungs appear on record and the rare earths are believed to be relatively nontoxic. However, skin changes have been described following exposure to some of the rare earths (7)(9). The chlorides of the rare earths may cause eye irritation and transient conjunctivitis. Corneal damage has been described with terbium and opacities have been noted with lanthanum (15). Intratracheal administration of the oxide of yttrium, neodymium and cerium in rats produce lung granulomas (7)(9). In large quantities inhalation may produce an acute chemical pneumonitis and bronchitis in animals (11). In other studies when rare earths were inhaled or injected by intratracheal routes into experimental animals there was no evidence of pulmonary fibrosis or other types of pulmonary reaction (10).

Cochran, et al. reported that lanthanum compounds exhibited low toxicity when administered orally to rats (4). Mice exposed to gadolinium oxide aerosol for 20-120 days demonstrated an increased number of deaths due to pneumonia five weeks after exposure. There was a trend toward shorter life spans in mice who survived exposure (2). There was also evidence that this compound was cleared completely from the lung. Histological features supported the evidence of its low-grade toxicity. There were focal areas of interstitial thickening and areas of macrophage accumulation containing rare earth dust particles. An unusual histological feature was pulmonary calcification in the region of the outer basement membrane and elastic lamina of small pulmonary vessels of exposed mice (2).

Schepers introduced a blend of rare earths with a high oxide content into the lungs of guinea pigs by intratracheal injection and noted fatal chemical pneumonitis in one-third of the animals. In those that survived, cellular eosinophilia

was a prominent feature (17). Most of the dust was trapped within areas of focal atelectasis, but no pulmonary fibrosis was noted. At one month, there was evidence of intraalveolar accumulation of pigment and engulfment of dust by alveolar macrophages. There was some dust transport to perivascular lymphatics. After one year, in animals that survived, there was peribronchial accumulation of dust and minimal scarring. In animals studied at 570 days, there were perivascular pulmonary granulomas without much pigment noted. Hilar lymph nodes showed focal aggregation of rare earth dust without inflammatory reactions. When blends of rare earth compounds, predominantly composed of fluorides, were introduced intratracheally, an acute transient chemical pneumonitis was produced followed by a subacute bronchitis and bronchiolitis (16). Graca et al. did a comparison study of stable rare earth compounds and found only transient but no permanent pulmonary changes (5)(6).

Clinical Description

There are no symptoms or abnormal physical signs or alterations reported for rare earths. No change in pulmonary physiology has been attributed to these inhaled dusts.

X-ray appearance

Hueck and Hoschek reported that 3 of 67 persons working in a photographic department of an offset printer, and in contact with carbon arc lamps, demonstrated opacities on chest x-ray similar to those of baritosis; they believed that the changes were due to cerium and other rare earths (10). In order to increase the brightness, the rods in arc lamps were equipped with cored carbon. An essential component of the rods is made up of rare earth fluorides. Parkes reported a similar case of an individual with dense opacities on chest x-ray who worked with cerium dioxide for six years (14). A French report describes two subjects with a miliary disease on chest x-ray, possibly due to the inhalation of cerium oxide (13).

Diagnostic Criteria

Differential diagnoses similar to other high-density dusts are in order. One may demonstrate radioactive thorium-228, in the expired breath by whole-body counter (14). Perhaps most important, a detailed occupational history will

establish the diagnosis of rare earth pneumoconiosis.

Analysis of tissue for rare earths by a quick and inexpensive means is not available; it is complex, especially when identifying for specific rare earths. Total rare earths content can be found by chemical methods (11). Absorption and x-ray fluorescence spectra can also be used for identifying a variety of rare earths (11). Flame photometry is not suitable for most rare earths because of interferences, but it can be used for lanthanum, neodymium, and ytterbium (12). Spectrographic analysis can be used for identifying rare earths especially when they are present in trace amounts. With the exception of cerium, atomic absorption spectrometry is the method of choice for quantitative determination for rare earths (11).

Method of Prevention

Environmental control is mainly designed to decrease inhalations since ingestion is harmless. Heated rare earths may give off toxic fumes that should be controlled. Dusts should be ventilated adequately (11). There is no TLV for any of the rare earths elements, although yttrium has an arbitrary TLV varying between 1 and 5 mg/m³, which was based on no clinical experiences or inhalation experiments (11). The TLV for yttrium can probably be applied to all rare earths. Gloves, protective eye wear and other protective equipment is necessary to prevent skin contact, especially with terbium. Employees with corneal injuries, kerato-conjunctivitis or conjunctivitis should not be exposed to the dusts. When there is thorium exposure, the amount of α -emitting radon daughters in air should be kept as low as possible, although no specific level has been yet generally agreed on.

Research Needs

Since there have been so few clinical pathologic studies available it is obvious that more information is needed. Little is known about the potential health effects of coexisting thorium (an α -particle emitter) and its decay chain. High concentrations of thoron daughters have been observed in thorium mining (1).

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SECTION III
OCCUPATIONAL ASTHMA AND RHINITIS

OCCUPATIONAL ASTHMA AND RHINITIS

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INTRODUCTION AND DEFINITION

Asthma is a common disease which affects 8 to 10 million people in the United States. It is high on the list of diseases requiring medical and hospital care and causes considerable loss of work and incapacity. The prevalence of allergic rhinitis is almost certainly higher and results in distress, discomfort, and work inefficiency. The proportion of this large population whose disease is due to occupational exposure is not known with certainty; indeed, accurate prevalences are difficult to determine. Crude overall estimates have varied considerably from 2% of all cases of asthma (20) to 15% of all male cases of asthma in Japan (23). Whichever of these figures is used to assess its impact in the United States, there is no doubt that occupational asthma causes a significant social hardship and a large economic loss.

Occupational asthma and rhinitis are different from the other forms of the disease only in that they are provoked by agents present in the workplace. Precise definitions of the diseases, however, have proven to be difficult. There have been a number of attempts by learned groups to define asthma in strictly objective terms; none have been entirely successful. Particularly difficult has been the differentiation of chronic bronchitis from asthma and the determination of the degree of airways obstruction and the degree of reversibility that must be present in order to make the diagnosis. A joint committee of the American Thoracic Society and the American College of Chest Physicians has provided a clinical definition (1):

Asthma: A disease characterized by an increased responsiveness of the airways to various stimulæ and manifested by slowing of forced expiration which changes in severity either spontaneously or with treatment. The term asthma

may be modified by words or phrases indicating its etiology, factors provoking attacks, or its duration.

A panel of the Allergy Foundation of America proposed (3):

Asthma is defined as recurrent episodes of wheezing or dyspnea characterized by a significant increase in resistance to airflow. Spontaneously or following treatment, periods of complete or almost complete freedom of symptoms occur accompanied by a substantial decrease in resistance to airflow. A person shall be said to have asthma when the following criteria are met: (1) recurrent episodes of wheezing or dyspnea, (2) objective evidence by pulmonary function test of significantly increased resistance to airflow during episodes and of improvement when the patient is symptom free, either spontaneously or as a result of optimum treatment. Several measures of airflow are acceptable: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak flow or maximum mid-expiratory flow. The following standard is tentatively adopted: the measure of flow should be less than 50% of predicted normal during a symptomatic episode whereas it should improve to more than 80% of predicted normal when the patient is symptom free.

The second definition attempts to define a degree of airways obstruction and reversibility. However, the figures quoted are arbitrary and may be considered by some to be unduly stringent, thus excluding some individuals from the diagnosis who genuinely have the disease. In addition, the definition begs the question of what is predicted normal, implying that normal is one figure whereas, in fact, it is a range usually accepted to include 95% of the population. Thus assuming that an individual, before developing asthma, was in the upper 5% of the population with respect to predicted values, he would require

an appreciable decrease in function before his flow rates decreased to less than 50% of the mean predicted normal value. To both these definitions should be added an exclusion—that the symptoms and signs are not due to cardiovascular disease. This is appropriate as paroxysmal nocturnal dyspnea due to left ventricular failure or intermittent small pulmonary emboli may provoke changes very similar to those of asthma.

Occupational rhinitis is easier to define than is occupational asthma. It can be said to be the episodic work-related occurrence of sneezing, nasal discharge, and nasal obstruction. Occupational rhinitis may co-exist with occupational asthma.

LIST OF CAUSATIVE AGENTS

The list of known agents associated with the development of occupational asthma and rhinitis continues to expand and any current list will, of necessity, be incomplete. It is recognized that an individual with an atopic background may become sensitized to virtually any natural product of appropriate antigenicity and particle size. With respect to synthetic agents, atopy is probably of less importance although bronchial hyperactivity in atopics probably makes them more susceptible to agents causing occupational asthma, regardless of mechanism. As new chemical processes are introduced, the list of agents capable of causing occupational asthma becomes longer. Causative agents of natural origin are found in organic dusts. These are inevitably less well characterized than those synthetic chemicals which cause problems. Because of this, the two are considered separately in the following list:

List of Causative Agents

Natural Products

1. Vegetable gums
2. Flax seed
3. Castor bean
4. Soybean
5. Natural glues
6. Animal danders and other animal antigens
7. Coffee bean
8. Insect debris
9. Detergent enzymes
10. Grain dusts and grain products
11. Orris root
12. Flour

13. Papain
14. Mushroom dust and moldy compost
15. Wood dusts
16. Natural resins
17. Animal fat, oil, and products
18. Fish meal and emulsions
19. Tobacco dust
20. Pancreatic extracts

Synthetic Products

Inorganic

1. Platinum, complex salts
2. Nickel salts
3. Chromium salts
4. Sodium and potassium persulphates

Organics

1. *Diisocyanates*
toluene
diphenylmethane
hexamethylene
2. *Anhydrides*
phthalic anhydride
tetrachlorophthalic anhydride
trimellitic anhydride
3. *Amines*
aminoethyl ethanolamine
dimethyl ethanolamine
ethylene diamine
paraphenylenediamine
diethylene triamine
diethylene tetramine
4. *Pharmaceuticals*
penicillins
ampicillin
spiramycin
phenylglycine acid chloride
sulphathiazole
bromelin
amprolium hydrochloride
sulphone chloramides
5. *Miscellaneous*
formaldehyde
piperazine
organophosphorus insecticides
pyrolysis products of polyvinyl chloride
alkylaryl polyether alcohol
tartrazine
products of heated adhesives

OCCUPATIONS AND POPULATION AT RISK AND PREVALENCE OF DISEASE

In order to develop occupational asthma and rhinitis, the worker must first become clinically sensitized either by immunologic or nonimmunologic mechanisms. Sensitization is a function of the dose, characteristics of the agent, and the individual's own responsiveness. The dose of the agents required to sensitize is not known, but is almost certainly higher than the dose required to elicit symptoms in the already sensitized individual. The prevalence of the disease observed in any population thus depends on the interaction of these variables together with the population selection phenomena discussed below.

Sensitization to natural products occurs most readily in the atopic segment of the population which is estimated to comprise between 10% and 20% of the total population (45). This proportion of the work population might, therefore, be expected to have a higher risk of becoming sensitive to organic dusts if suitably exposed. There are serious problems in taking such a simplistic approach. Both pre-employment and postemployment selection affects the constitution of the residual worker population in the involved industries. An atopic individual may personally decide, or be advised, that his risks of occupational sensitization are considerable and so might choose not to work in a particular industry. Even in the absence of a specific sensitization the atopic, because of the hyperirritability, of his airways, may leave a dusty or irritating work environment within a short time of starting work. Both these factors tend to reduce the proportion of the high risk atopic segment of the population in some industries. Loss from the work force of these high risk individuals also prevents accurate determination of the true impact of occupational sensitizers and tends to give a falsely low estimate of prevalence. In occupational asthma caused by synthetic products, these factors probably have somewhat less of an impact as both atopic and nonatopic individuals develop asthma and rhinitis. Accurate prevalence data are, however, confounded by loss from the work force of the sensitized individual who will often seek alternate employment after recognizing the occupational nature of his problems. Factors determining whether a sensitized worker will leave a particular industry also vary. These in-

clude the degree of incapacity, the personal investment in terms of training and education, and the availability of alternate employment. Thus the work forces studied represent survivor populations, and this results in misleading prevalences.

It is well recognized that environmental allergens—to which we are all exposed—have differing potencies as sensitizing agents. This also applies to occupational agents although because the dose received is much more variable both within an industry and from industry to industry, it is difficult to separate dose effect from sensitization potency of the agent. In addition, changes in work practices and environmental control will influence observed results.

The prevalence of occupational asthma and rhinitis varies markedly from industry to industry. Animal handlers and breeders have an approximately 6% risk of asthma and a 9% chance of rhinitis by becoming sensitized to the animals to which they are exposed (26); printers, a 19% chance of developing asthma when exposed to gum-acacia (19); and up to a 75% sensitization to bacterial proteolytic enzymes was reported prior to environmental control in the enzyme detergent industry (48). In the case of synthetic agents, toluene diisocyanate has produced prevalences ranging from about 5% to 15% (31). When given sufficiently long exposure, the complex salts of platinum result in virtually 100% sensitization (41). These facts already noted, together with a complete lack of prevalence data with respect to the majority of agents, prevents any assessment of the overall prevalence of occupational asthma and rhinitis. The populations at risk are presented on page 464.

EPIDEMIOLOGY

The questions which epidemiologic studies of occupational asthma and rhinitis need to answer are:

1. What are the prevalences of the diseases in different occupations?
2. Is there a relationship between dose received, either cumulative or peak concentration, and the prevalence of sensitized workers?
3. What is the relative risk of sensitization of nonatopic compared with atopic workers? Are there other personal factors

POPULATION AT RISK

<i>Industry or Occupation</i>	<i>Agent or Agents</i>	<i>Number</i>	
printers, paper products manufacture	vegetable gums	6,000	
	natural glues	130,000	
grain handlers	grain dusts, insect debris	97,000	
lumber & woodworking industries	wood dusts	1,646,000	
	millers	flour, insect and mite debris	16,000
bakers	flour, insect and mite debris	230,000	
veterinarians	animal danders	23,000	
animal breeders and handlers	animal danders	2,000,000	
	animal antigens		
laboratory workers	animal danders	10,000	
	animal antigens		
farm workers	animal danders	4,500,000	
	vegetable dusts		
	organophosphorus insecticides		
vegetable oil production	flax seed	1,200	
	castor bean		
	cotton seed	5,500	
detergent industry	proteases	5,700	
food additive production	proteolytic enzymes	?	
	tartrazine	14,000	
coffee processing	green coffee beans	12,900	
*beauticians/cosmetologists	orris root	?	
	paraphenylene diamine	1,000	
	sodium and potassium persulfate	13,500	
**hospital workers	formaldehyde	275,000	
	pharmaceuticals		
	penicillin	3,500	
	ampicillin	1,300	
†pharmaceutical workers	sulphatriazole	1,000	
	bromelin	?	
	amprolium hydrochloride	?	
	sulphone chloramides	?	
	piperazine	700	
	solderers, electrical and electronic industry metal fabrication	penicillin	6,000
		ampicillin	2,000
		spiramycin	?
		phenylglycine acid chloride	?
		colophony resin	—
amino ethyl ethanolamine		1,500	
	alkyl aryl polyether alcohol	2,000	

POPULATION AT RISK (Continued)

<i>Industry or Occupation</i>	<i>Agent or Agents</i>	<i>Number</i>
††leatherworkers	formalin	11,000
	chromium compounds	2,000
platinum refiners	complex salts of platinum	300
metal platers	salts of nickel	10,000
	salts of chrome	1,400
fur dyers	paraphenylene diamine	4,000
paint sprayers	dimethyl ethanolamine	3,700
	diisocyanates	10,000
plastics industry primary manufacture and use: mainly epoxy resins and polyurethane	diphenyl methane diisocyanate	1,000
	hexamethylene diisocyanate	500
	phthallic anhydride	4,000
	tetrachloro phthallic anhydride	20
	diethylene triamine	5,000
	diethylene tetramine	100
	piperazine	500
rubber industry	ethylene diamine	5,000
	diisocyanates	2,000
foundry industry	diphenylmethane diisocyanate	1,200
insulation workers	diisocyanates	3,000

*There are 280,000 beauticians in the United States; most are not associated with exposure to listed agents.

**There are approximately 2.5 million hospital workers in the United States.

†There are 112,000 pharmaceutical workers in the United States.

††There are approximately 20,000 workers in the leather processing industry.

which relate to the risk of becoming sensitized?

4. What is the long-term prognosis of sensitized workers who cease exposure?

Though there is a large literature relating to occupational asthma and rhinitis, this consists largely of case reports and detailed investigations of the involved mechanisms. Essentially, the four questions posed above remain unanswered.

Prevalence data are difficult to obtain and require large, complex, and expensive surveys. Prevalences have been reported from some industries, but invariably there are serious problems in interpretation. A major problem is that the populations studied are survivors of the effects of the work environment, sensitized individuals having already left the industry before the study commences. In a follow-up study of a TDI-exposed population, Wegman et al. found that only 45% of their original study group was still employed (47). Of those who left, 80% did

so voluntarily; how many for reasons of sensitization is not known. The extent of this attrition of worker populations can thus be large and effectively prevent realistic estimates of sensitization rates.

Prevalence data are often generated by questionnaire studies. While these can provide estimates of the impact of the working environment on the respiratory tract, they do not provide reliable information concerning the prevalence of asthma. The main reason is that questions relating to dyspnea, chest tightness, cough, and wheezing do not differentiate asthma from chronic obstructive pulmonary disease. A study of 300 grain elevator workers provided prevalences of 76% cough, 49% chest tightness, 42% wheezing, and 45% dyspnea (15). This clearly shows that grain dust frequently causes respiratory problems but does not indicate the proportion of the symptomatology due to grain dust related asthma.

There is general agreement that reversible airways obstruction is the prime characteristic of asthma. Pulmonary function surveys of worker groups have been conducted; however, almost invariably, measurements were made at only one time. An index, such as the ratio of the FEV₁ to FVC, will provide evidence of airways obstruction but without any information concerning reversibility. There is thus no way to differentiate the nonreversible airways obstruction of chronic obstructive pulmonary disease from asthma if workers are only studied once. Pre- and post-shift measurements are essential. A comparison of two studies of meat wrappers' asthma due to the pyrolysis products of PVC will serve to illustrate the problem of relating questionnaire data to objective airways changes. Using questionnaire data, Andrasch et al. reported a prevalence of 69% of respiratory symptoms in 96 exposed workers (4). They proved that heated PVC could cause decrements in flow rates in small number of workers by bronchial provocation testing. It is, however, not possible to extrapolate this observation and to account for all or most of the respiratory symptoms in the overall worker group by assuming that they likewise developed airways obstruction on the job. This is shown by a study of a different group of 30 meat wrappers by Krumpel et al. (24). In addition to questionnaire data, they carried out detailed pulmonary function testing after a two-day vacation and again after working one shift or working for the whole week. By questionnaire, 23% of the wrappers reported work-related asthmatic symptoms; however, significant changes in parameters of airflow were not found following exposure on the job in any worker. Both these studies lack measurements of exposure to fumes. Peters et al. reported decrements in flow rates over a shift in workers exposed to TDI (38). They found a mean fall in FEV₁ for the whole group of 0.19 liters. This illustrates two problems: first, the reporting of group mean changes does not provide evidence of the prevalence of asthma, nor, second, how much of a decrement over a shift is needed to make a diagnosis of occupational asthma. The mean decrement reported is very small and though statistically significant, is of the same order of magnitude as the upper limit of variability of a single spirometric measurement. There is a need to develop some generally agreed upon criterion of function decrement in order

to determine the prevalence of asthma in worker populations; statistically significant change does not provide a satisfactory definition.

There is even less good information available to answer the remaining three questions. There is evidence that decreases in environmental concentration of agents results in lower prevalences of sensitization to TDI (40), and that control of environmental *B. subtilis* enzymes in the enzyme detergent industry has reduced sensitization (28)(48). There is, however, no available study of any agent which fully answers the question of the relationship of sensitization rate and exposure.

Most studies of sensitization to naturally occurring agents indicate that the atopic segment of the population is at greater risk of sensitization than the nonatopic. Nonatopics may, however, sometimes develop occupational asthma due to exposure to natural products. With respect to synthetic agents, atopy appears to be a much less significant risk factor. There is need for considerably more research in this area to evaluate the likely impact of pre-employment screening. What little data are available on the long-term effects of occupational asthma after ceasing exposure are considered in the section on prognosis. It will be seen from this short account that information is incomplete on the epidemiology of occupational asthma and rhinitis.

PATHOLOGY

Although the amount of available evidence is scant, occupational asthma is considered to be pathologically identical with asthma in general. The pathology of asthma has been studied from three main sources:

1. Autopsies of individuals dying in status asthmaticus, and occasional autopsies carried out on individuals with active asthma who have suffered a traumatic death. The limited amount of the latter material shows less severe changes than those found in status asthmaticus but confirms the essential findings.
2. Biopsy material taken during acute asthmatic attacks and when in remission. This material is limited for obvious reasons.
3. Studies of sputum samples, particularly by section rather than by smear.

The following account is derived from a composite of these sources. The essential path-

ological change found in asthma is a reduction in the lumen of the bronchial and bronchiolar airways. Partial obstruction of an airway results in a nondestructive "physiologic" emphysema with resulting over-distention of the lung. Complete obstruction produces focal areas of collapse which are commonly found in individuals dying in status asthmaticus. Narrowing of the airways is due to bronchial muscle spasm, to an increase in the thickness of all layers of the airways, and to obstruction of the lumen by plugs of viscid sputum. Histologically there is increased thickness of the bronchial muscular layer which is a useful point in the differentiation of chronic asthma from chronic bronchitis. Bronchial mucous glands are hypertrophied and the mucosa is thickened. The thickening is due to a combination of edema, capillary dilatation, and cellular infiltration in the submucosa. The cellular infiltrate is mixed, and includes eosinophils, plasma cells, and lymphocytes. There is characteristically marked thickening of the basement membrane of the bronchial mucous membrane (16). Immunoglobulins, particularly IgM, and the third component of complement have been demonstrated in this region in some patients (8)(9). In severe asthma and in status asthmaticus there is appreciable shedding of mucosal cells into the lumen of the bronchus. The epithelium may lose virtually all columnar cells and consist only of basal cells. Experimental evidence suggests that in remission, a completely new epithelium may develop from these residual basal cells (49). The lumina of the bronchi contain plugs of sputum. In asthma, this has a characteristic nonhomogeneous appearance on staining and contains mucus, a serous exudate, shed epithelium, and inflammatory cells—particularly eosinophils. The sputum may contain creola bodies (clusters of shed epithelial cells) and Charcot-Layden crystals (elongated hexagonal, bipyramidal crystals derived from eosinophils). Examination of expectorated sputum in the living asthmatic will reveal these components and also may show Curschmann's spirals which are casts of small airways. Although there is a paucity of data on the anatomy of the asthmatic airways between attacks, available evidence indicates there is little residual abnormality in the bronchial mucous membrane at this time.

PATHOGENESIS AND PATHOPHYSIOLOGY

Research in recent years has resulted in a much clearer understanding of the pathogenesis of asthma in general; research into occupational asthma has contributed much to this understanding. The pathogenetic mechanisms of asthma are highly complex and which of the many abnormalities demonstrated is of greatest importance is not known. Further, in many cases of asthma the mechanisms are still unexplained. There are three main mechanisms involved in the generation of asthma.

Irritant Factors

Hyperreactivity of the airways as evidenced by methacholine and histamine provocation challenge testing is characteristic of the asthmatic state. Thus an asthmatic responds to between one hundredth and one thousandth of the dose of these agents which will produce airways narrowing in a normal individual. Though the reactivity is greatest when an individual is suffering recurrent asthma attacks, the hyperreactivity remains between attacks although it may diminish. Atopic individuals who have not suffered from asthma for a long period of time show reactivity midway between normals and active asthmatics. In occupational asthma, this decrease in hyperreactivity has been demonstrated following removal from the agent in question. The reasons for the hyperreactivity of the airways in asthmatics are not known; however, it is generally considered to involve an alteration in the homeostatic mechanisms which control the airways' smooth muscle tone. As a consequence of this hyperreactivity, any irritant agent—such as an organic dust or a chemical which may have little or no effect in healthy people—can precipitate episodes of airways obstruction in workers either with asthma or with a past history of asthma. Such episodes can occur even though the agent is present in very low concentration. A mechanism involving stimulation of irritant cough receptors by inhaled material and mediation by the vagus nerve is prominent among those pathogenetic processes producing airways obstruction in asthmatics. For example, the increase in airways obstruction following inhalation of some irritants can be inhibited in ex-

perimental animals by blockage of the vagus nerve. In man, prior inhalation of atropine followed by the inhalation of the irritant would also abrogate the response (30). Based on anecdotal evidence, it is likely that many agents can induce airways obstruction in asthmatic subjects by means of such irritant receptor stimulation. The same agents may act as both irritants and sensitizing agents under different conditions. For example, the inhalation of large amounts of green coffee bean or grain dust may result in an irritant type of rhinitis and conjunctivitis, possibly with some minor airways obstruction. But repeated inhalation of small amounts of these substances may sensitize (22). In the latter case, re-exposure to minute concentrations incapable of producing an irritant effect, will result in upper and lower airways symptoms in these individuals based on IgE mediated allergic effect. Similarly, high concentrations of toluene diisocyanate will cause mucosal irritation in any worker but a "reactor" will respond to barely detectable levels (7).

Allergic Factors

IgE mediated allergic reactions have been strongly implicated in the pathogenesis of many forms of occupational asthma due to natural inhalants and in some due to synthetic chemicals. Epidemiologic surveys employing skin test reactions and respiratory questionnaires have also indicated a positive association between the atopic predisposition and susceptibility of bronchial constriction in the case of natural inhalants. This association between atopy and sensitization to occupational agents has not been as clearly shown in the case of synthetic chemicals, and many individuals with definite asthmatic responses to simple chemicals give no past history of allergic problems in either themselves or in their families. In IgE mediated asthma, there is generally a latent period of weeks, months, or even years between initial contact with the occupational agent and the development of overt symptoms. Only a small proportion of those individuals exposed (i.e., mainly those with a genetically determined predisposition to produce specific IgE antibodies) will generally develop the disease in the case of naturally occurring occupational sensitizers. Skin prick or intradermal tests with the appropriate natural occupational product or allergen are almost always positive as are passive transfer studies in man or primates.

Specific serum IgE antibodies have also been demonstrated by *in vitro* tests employing a number of natural occupational agents such as coffee and castor beans (22). In the case of synthetic sensitizers, skin tests may present a problem in that the agent may be very irritating. In some situations, conjugation of the chemical to a carrier protein (such as human serum albumin) has enabled positive skin tests to be demonstrated in some of these individuals and again specific serum IgE antibodies have been demonstrated. IgE antibodies may be measured by several assays, the most common of which is the radioallergosorbent test (RAST). The presence of circulating IgE antibodies seems to correlate well with the development of immediate or early onset asthma due to natural products but not with the late onset type of asthma. Where demonstrated, as against phthalic anhydride (27), trimellitic anhydride (50), and the complex salts of platinum (13), IgE antibodies directed against synthetic chemicals usually correlate well with the clinical presentation. Toly-reactive antibodies have been demonstrated in some reactors to TDI (21), but in many others they are undetectable, suggesting the possibility of two different mechanisms of sensitivity reaction to this agent.

The mechanisms involved in late onset asthma, with a lag period of several hours between exposure and onset of symptoms, are not clearly understood. IgE mediation has been suggested by some researchers in the case of late reactions to pollens (42), but this is by no means certain. It is possible that the use of tests to detect circulating immune complexes and the rheumatoid factor, and studies of antibodies of the homocytotropic short-term sensitizing IgG type (5)(33) may shed some light on the mechanisms involved in this more insidious late onset occupational asthma. This remains conjectural. The same can be said for *in vitro* assays for cell-mediated immunity by testing for lymphocyte transformation and the macrophage migration inhibition factor (MIF) production which also might theoretically be associated with some forms of late onset occupational asthma. In IgE mediated asthma and rhinitis, symptoms result from the classic and well known release of mediators from tissue mast cells and basophils subsequent to IgE and antigen interactions at the cell surfaces (39). These mediators include, among others, the slow reacting substance of anaphylaxis (SRSA, now refer-

red to as leukotrienes) histamine, and the eosinophil chemotactic factor of anaphylaxis (ECFa). These act on secondary target tissue to produce the clinical picture of asthma and rhinitis. They act primarily on vascular endothelium to produce edema, by inducing infiltration of inflammatory cells into the mucous membrane, in addition to directly causing smooth muscle spasm. This type of IgE dependent mediator release is noncytotoxic and essentially represents a form of immunologically induced secretion from mast cells. From a biochemical viewpoint, the studies of mediator release employing human lung tissue agree with those obtained using lung tissues from other species, human peripheral leukocytes, and rat peritoneal mast cells. The union of an antigen with IgE at the cell surface is followed by an intracellular calcium-requiring activation of an esterase followed by autocatalytic feedback activation of a proesterase and an energy requiring step which utilizes glycolysis or oxydative phosphorylation. This is followed by an intracellular step requiring calcium, a step suppressed by increased concentrations of cyclic adenosine 3', 5' monophosphate (cyclic AMP), and finally the secretion of mediators. It is thought that IgE receptors act as a concentration mechanism which juxtaposes two molecules of this trace immunoglobulin side by side to permit bridging by the antigen. Such bridging is held to produce a membrane perturbation which initiates the sequence of events.

Pharmacologic and Other Mechanisms

The occupational causation of asthma by some agents has been clearly demonstrated by carefully controlled bronchial provocation tests, yet the pathogenetic mechanisms involved are still unknown. In some of these cases, bronchial hyperreactivity to methacholine has been demonstrated, but this is likely to be a secondary phenomenon rather than the initiating mechanism because a return toward normal occurs following avoidance of the agent (25). With other agents, immunologic hypersensitivity may be involved, but the evidence available is either conflicting or very scanty. For instance, in asthma due to synthetic chemicals, the appropriate reactive group may not be present on the protein-hapten conjugates used for the tests, or the simple chemical may alter host proteins to create neoantigens which induce a subsequent immune response. In the case of some organic dusts, the

causative antigen may represent only a minor component rendering both skin and *in vitro* tests relatively insensitive.

To explain the pathogenesis of asthma due to these agents, direct pharmacologic action on the airways and nonimmunologic release of histamine and other spasmogens has been postulated. *In vitro* experiments have shown the direct release of histamine by the complex salts of platinum (34) and by aqueous extracts of western red cedar (18). However, more recent evidence has demonstrated specific IgE sensitivity both by passive transfer in man (37) and by RAST test (13) in the case of the former. Grain dusts have been shown to have the potential to activate the alternate pathway of complement, with the potential for nonimmunologic release of mediators from mast cells by the anaphylotoxins generated by this reaction (32). Toluene diisocyanate has been shown by *in vitro* testing to act as an inhibitor of the stimulation of beta adrenergic receptors (6)(16), thus raising the possibility that it could interfere with autonomic control of airways tone in the direction of favoring bronchoconstriction.

These hypothetical mechanisms raise two major questions. Why does only a proportion of the exposed population respond? Why is there a latent period between first exposure and the development of symptoms? Attempting to answer the first question, it could be suggested that the known hyperirritability and hyperresponsiveness of the airways of an atopic individual would be expected to result in a response to a much smaller release of mediators than would a nonatopic individual. Under these circumstances only the atopic segment of the population should respond in this way. Yet there is no doubt that, though less common, occupational asthma does occur in nonatopic workers. In order to support this hypothesis, some mechanism must be demonstrated which results in the airways of a nonatopic individual becoming more nonspecifically reactive. Or there is a genetically determined factor, not associated with atopy, which determines bronchial hyperreactivity. The second question concerning latent period is difficult to answer. There is an implication of a nonimmunological change in airways, responsiveness between first exposure and first development of symptoms. There is no information to explain how this is brought about. However, possible theoretical mechanisms ex-

ist which may account both for the latent period and for the occurrence of changes in nonspecific reactivity in nonatopic individuals. One author has noted that some individuals with occupational asthma give a history of what sounds like a respiratory virus infection a short time before the onset of work-related symptoms. This information, by its very nature, is nonobjective and could be inaccurate. It has been demonstrated that the airways of the nonatopic become hyperactive in a similar way to the airways of an atopic individual following respiratory infections (17). Thus a change in airways reactivity following an infection could lead to a self-perpetuating asthmatic condition when repeatedly triggered by an industrial agent. This mechanism could account for both the occurrence of asthma in the nonatopic and also for the latent period, the latter being the time between the first exposure to the occupational agent and the first occurrence of an appropriate respiratory infection. Similarly, the airways of an atopic become more sensitive to methacholine following challenge by an allergen to which he is sensitive (12). The airways of an atopic individual may, therefore, vary considerably in their nonspecific responsiveness, depending on the presence or absence of aeroallergens in the nonwork environment. Coincidental exposure to an aeroallergen, which in itself may result in mild or subclinical effects, and an occupational agent could result in an asthmatic attack. The hyperreactive state initiated by the environmental aeroallergen could then be perpetuated by continued industrial exposure even after the aeroallergen was no longer present. Though attractive, there is no evidence to directly support this hypothesis.

CLINICAL DESCRIPTION

Types of Asthmatic Reactions Associated with Inhalation of Occupational Products

Provocation challenge testing with many types of occupational products has resulted in different patterns of airways response. These are immediate responses, occurring within minutes of exposure; nonimmediate, or late responses, which have a latent period of several hours between exposure and first airways changes; biphasic responses which are a combination of both early and late; and at times, sustained or recurrent asthmatic reactions (35). There is no difference in the clinical manifestations of these reactions and those noted after experimental in-

halation of natural common aeroallergens such as pollen and mold. The experimental asthmatic reactions are thought by most investigators to serve as the clinical laboratory correlates of the immediate and late asthmatic reactions which are noted in an ordinary clinical setting.

Symptoms, Signs, and Natural History

Symptoms are characterized by dyspnea, wheezing, chest tightness, and cough of an episodic nature. The history, however, provides the most important diagnostic clue, and the aphorism "listen to the patient, he is telling you the diagnosis" truly applies in the context of occupational asthma and rhinitis. Immediate reactions usually occur within 10-20 minutes after exposure and may last for several hours or until leaving work. They are usually not associated with systemic reactions or marked changes in the white blood cell count and are characterized by only moderate or slight eosinophilia. They are reversible by isoproterenol and can be inhibited by prior inhalation of cromolyn sodium but not by inhaled corticosteroids. The occurrence of late reactions, after the worker has returned home, often makes diagnosis and recognition of occupational asthma more difficult. In some late reactions, bronchospasm may be reflected by cough, chest tightness, or dyspnea without significant wheezing—possibly indicating small airways obstruction. In general, late reactions develop slowly and become progressively worse. They may not be clinically obvious except on exertion or until fully developed. They may require a latent period of 4-8 hours before appearing and may last from 24 to 96 hours. These reactions may also be associated with systemic symptoms such as malaise and myalgia. Fever and leukocytosis may be present, especially if a systemic reaction occurs, and there may be marked eosinophilia. Late reactions are, as a rule, poorly and only temporarily reversible by isoproterenol. They are, however, reversible by inhaled or systemic corticosteroids and may be prevented by the prior inhalation of cromolyn sodium. Although the taking of a careful occupational history can often uncover symptoms suggestive of occupational asthma, other diagnostic tests depend on the availability of proper facilities. For example, in the case of bronchial provocation challenge testing, or *in vitro* and related tests, facilities and adequately trained personnel (to perform these procedures) are often lacking in many medical centers.

Appropriate Laboratory Investigations

Pulmonary Function Studies

Demonstration of reversible airflow obstruction is a prerequisite for making the diagnosis. Determination of the forced expiratory volume in 1 second (FEV_1) or other indices of flow rates (such as the forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25-75})) are relevant and reproducible tests. The latter determination is more sensitive but has greater variability. Regardless of the test employed, measurements should ideally be made both before and after work exposure. The most frequently employed function tests used to detect an asthmatic response in workers are those that involve demonstration of limitation in maximal expiratory flow rates either by traditional volume/time plots or by maximal expiratory flow/volumes curves, using an electronic spirometer or pneumotachograph. These tests have also proven useful in field studies. Many centers have included relatively newer methods of detecting airways obstruction (such as closing volume) in their epidemiologic field testing procedures. The additional benefits from these newer tests are not certain. Proper timing in the use of pulmonary function tests may also be crucial in the diagnosis of occupational asthma. Measurement of both pre- and post-shift ventilatory function of the worker usually demonstrates an acute asthmatic effect resulting from exposure under normal job conditions. In interpreting these data, account should be taken of the normal diurnal variation in ventilatory function.

Bronchial Provocation Tests

Two types of bronchial challenge tests are useful in the diagnosis of occupational asthma. These measure either nonspecific bronchial reactivity to methacholine or histamine, or specific reactivity to the agent in question. Demonstration of nonspecific airways hyperirritability tends to confirm that the worker's complaints are real and that he does, indeed, have asthma. Methacholine challenge should be carried out using the protocol developed by the program directors of the Asthma and Allergy Disease Centers (10). Challenge with a specific agent provides a means of proving the occupational nature of the worker's asthma. This is important if a change of job is being considered and can be important for

medico-legal reasons. In addition, other less direct approaches such as demonstration of specific IgE mediated skin reactivity or RAST testing are not available with respect to many agents. The object of the challenge is to mimic, under controlled conditions, workplace exposure and to monitor ventilatory function before and for several hours (preferably at least 24) afterwards. Concentrations of the agent should be measured and should not exceed those to which the worker is exposed in the workplace. It is essential to carry out a similar procedure with a control non-irritant, nonsensitizing material in order to evaluate any changes in pulmonary function observed with the test agent. A decrease of 20% in FEV_1 is a commonly used criterion for positive reaction.

Chest Roentgenograms

Chest roentgenograms are not of particular value in the diagnosis of occupational asthma and may only reveal the overinflation often found in asthma. They may, however, be of considerable importance in differentiating late onset asthma from hypersensitivity pneumonitis, which can present a similar clinical picture.

Skin Tests and RAST

In occupational asthma, skin testing can be of considerable diagnostic value where immediate wheal and flare hypersensitivity is involved and sufficiently purified skin test preparations are available. Skin testing can be helpful both in assessing the atopic status of the worker by using common aeroallergens and in attempting to determine the presence of a specific IgE antibody against the appropriate occupational agent. Any natural agent employed for skin testing purposes should be as well characterized and as purified as possible. This presents an enormous problem with some organic dusts because of their complexity. It is sometimes possible to use nonnatural agents in a very pure form as, for instance, ammonium hexachloroplatinate (36); others, such as dimethylethanolamine may produce wheal and flare responses in all individuals tested (46). Conjugation of a reactive chemical to a carrier protein, such as human serum albumin, can usually provide a usable skin test preparation. All skin test antigens should be nonirritant and nontoxic to normal individuals in the concentrations to be employed. They should always be evaluated initially

in very low concentrations, employing the prick assay rather than the intradermal method. While skin testing is more sensitive in demonstrating IgE mediated reactivity than *in vitro* methods such as RAST, the latter does have some advantages. It avoids the potential danger of a serious reaction following skin tests and is useful in individuals on medication which might interfere with skin reactivity or who have skin problems such as dermatographia or eczema which interfere with skin test interpretation.

Treatment and Prognosis

The treatment of occupational asthma does not differ from that of conventional asthma due to environmental pollens and molds. Basically it consists of the avoidance of known causative inhalants and the control of symptoms with conventional bronchodilators (preventives such as cromolyn sodium and corticosteroids if necessary). With proper diagnosis and permanent removal from the offending environment, the prognosis is good. The ultimate form of treatment in occupational asthma is removal of the affected worker from the job environment which, in effect, will usually result in a "cure." Symptoms will usually subside within a few days of ceasing exposure; however, this is not invariably the case. There is a lack of data on follow-up of occupational asthmatics who cease exposure. Collection of such data is fraught with difficulties. Patients are "lost" when they move to change employment, and some refuse to cooperate, particularly if litigation against a previous employer is involved. Some individuals with TDI induced asthma continue to complain of attacks long after leaving the industry. Is this a long-term effect of occupational asthma, or is it asthma of some other causation? Comparison of pre-employment function tests with similar tests carried out in 20 workers, who had ceased exposure to TDI from between 3 and 8 years because of sensitization, was made by Adams (2). Twelve of the 20 had FEV₁ and FVC values unchanged from their pre-employment levels; 6 had decrements up to 10% and 2 had larger decrements. Symptoms of dyspnea on exertion and chest tightness were reported by those with decrements of function. Thirty-eight workers with proven occupational asthma due to western red cedar were studied by Chang-Yeung (11). While the majority became symptom-free, eight continued to suffer recurrent asthma attacks

when evaluated after a mean of 1.6 years following cessation of exposure. It is of interest that seven of the eight were nonatopic and all but one gave a biphasic response on challenge at the time of diagnosis as compared with 50% of those who became symptom-free. There is a great need to develop data concerning the fate of occupational asthmatics when they cease exposure.

In cases where workers cannot be totally removed from the environment, a trial of a preventative such as cromolyn sodium or the long-term use of a theophylline preparation or inhaled corticosteroid might theoretically prevent immediate or late bronchial reactions. This form of preventive therapy is obviously no substitute for removal of the worker from the hazardous environment. Even though engineering methods and other dust and vapor suppressant measures are often effective in lowering workplace concentrations of the agent it must be recognized that in a sensitized worker even minute amounts of occupational agents can result in a response.* In this context, occupational standards such as 8-hour time-weighted-averages and ceiling levels have little or no meaning. In some situations temporary protection can be provided by the use of a respirator, however, this should not be considered as a long-term solution. If preventive and therapeutic measures are not effective, a final and agonizing decision often must be made involving the selection of another job for the worker. This often produces adverse domestic, financial, and family problems and provides multiple legal complications.

DIAGNOSTIC CRITERIA

History

The mainstay of diagnosis in occupational asthma remains that of obtaining a careful history and asking the all-important question "What is your occupation?" In view of the wide variety of agents that cause occupational asthma, many such cases will only be diagnosed if the possibility of a cause and effect relationship is first entertained and then sought by careful questioning. Occasionally, nocturnal cough rather than wheezing during the working day may be the presenting symptom. In other cases, symptoms may extend over the weekends and short holidays, effectively disguising the industrial ori-

*In rare cases, a level of exposure may be demonstrated at which flow limitation does not result.

gin of the disease. Education of physicians in the occupational causation of asthma and rhinitis is the key to more frequent recognition of this group of diseases.

Pulmonary Function Tests

Airflow obstruction upon exposure to an offending industrial agent, with reversibility, is a prerequisite for diagnosis. Ideally, such measurement should be made both before and after work exposure. While decrements of function strongly suggest the occupational origin of the asthma, they do not necessarily indicate which agent is responsible. This can be particularly difficult in a complex environment. Additionally, there is no general agreement on what decrement of function over a work shift is necessary to make a diagnosis of occupational asthma.

Bronchial Provocation Testing

Performed under properly controlled conditions, this remains the most certain way of confirming the occupational nature of a worker's asthma and of identifying the inhaled agent involved. Such provocation testing can clearly establish a cause and effect relationship but does not provide information with regard to the pathogenetic mechanisms. In performing such challenge testing one should carefully attempt to simulate the subject's work conditions with monitoring of exposure levels.

Skin Tests, RAST, and Precipitating Antibodies

Skin, prick, and intradermal tests are often useful both to assess the atopic status of a worker and to look for the early development of IgE mediated wheal and flare skin reactivity against the appropriate offending agent when an IgE mechanism is involved. Unfortunately, suitable skin test preparations are not available for many agents either because they are too irritant in themselves or too impure. *In vitro* procedures to detect IgE antibodies such as the radio allergosorbent test (RAST), enzyme-linked immunoassay, or polystyrene tube assay are also assuming increased importance in the diagnosis of occupational allergic disease. RAST is less sensitive and, therefore, of somewhat less value when compared to the skin test, but it does afford many advantages, including that of a non-invasive *in vitro* technique. Tests for the presence of IgG precipitating antibodies against organic

dusts and related natural products have generally not been useful in the diagnosis of occupational asthma. Precipitins, when present against organic dusts, are generally detected in both symptomatic and nonsymptomatic workers and often do not correlate with the presence of overt disease. They tend to correlate better with the extent of exposure (43).

METHODS OF PREVENTION

Prevention of occupational asthma and rhinitis will be considered under four headings.

1. **Recognition that a problem exists.** The list of known agents which can cause occupational asthma and rhinitis is long and is continually growing. It is important that the hazards associated with exposure to these agents are known, both by management and labor, so that appropriate steps may be taken. As it is inevitable that more sensitizers will be recognized in the future, industry must develop rapid and practicable means to detect them. Unfortunately, animal tests are not likely to be of value in this context.
2. **Prevention of sensitization.** There are two approaches to the prevention of sensitization, neither of which is entirely satisfactory. The impact of occupational sensitization falls most heavily on the atopic segment of the population. It is possible to conduct pre-employment screening to determine the atopic status of job applicants by family and personal medical history and by carrying out skin tests with a number of common aero-allergens. Such pre-employment screening should result in a much lower prevalence of occupational asthma and rhinitis, particularly following exposure to natural products. It is doubtful if it would have a significant impact on asthma and rhinitis due to synthetic agents. Though not strictly covered by the Equal Employment Opportunity laws, the exclusion of such a large segment of the population from work in certain industries might be considered discriminatory. While an atopic individual is likely to become sensitized following continued exposure to even minute amounts of a

natural product, sensitization in non-atopics may be dose-related. In both atopics and nonatopics, sensitization to synthetic agents may also be dose-related. There is a lack of objective studies to support this opinion, mainly because of the great difficulty in conducting such studies. Thus continuous personal exposure monitoring will be needed over a period of a year or more with follow-up of ideally 100% of the workers. Such a study is difficult to achieve. Changes in the prevalence of reported sensitization, coincidental with changes in environmental concentration tend to support this view even though the data are limited. Thus the number of sensitized individuals in a TDI plant fell as the average concentration of TDI decreased from 60 ppb in 1956 to less than 4 ppb in 1974 (40). Rates of sensitization of about 60-75% were reported due to exposure to *B. subtilis* enzymes in the detergent industry (29)(48); with environmental control and process changes, the rate is now of the order of 2% (28). Though encouraging, these studies should be interpreted with caution as population selection phenomena could have also played a significant part in reducing the prevalence of occupational rhinitis and asthma in the studied populations.

3. **Early recognition of sensitization and relocation.** Bronchial obstruction can be detected by changes in airways resistance (as measured by simple spirometry) often before overt symptoms develop. Thus, evaluation of pre- and post-shift FEV₁ at regular intervals should result in early detection of sensitized workers. Biological monitoring, either by skin tests or *in vitro* serum specific IgE assays, have also been suggested. The correlation of the latter with significant clinical symptomatology, and the fact that their sensitivity is lower than that provided by skin tests, suggest that *in vitro* assays would not detect clinical sensitization earlier than pulmonary function changes. While there is some evidence that positive skin tests may develop before respiratory sensitization (44), this is by no means proven with respect to occupational allergens. Workers should be educated

to report respiratory symptoms to the medical representative of their employer, their health and safety representative, and their personal physician. This would contribute to early recognition, yet affected individuals often try to conceal their problems. A major factor in this concealment is the fear of job loss—a very real fear. Some employers attempt to relocate an employee in a part of the plant where exposure to the offending agent does not occur; others terminate the worker's employment, which may lead to litigation. Before any worker education program can be successful, the problems of job security, relocation, and compensation need to be resolved.

4. **Prevention of reactions in the already sensitized.** Reduction of environmental concentrations of the agent to levels below which the sensitized individual would react is usually an unachievable ideal. The sensitized worker often responds to concentrations at the level of detectability, and in the context of occupational asthma, the customary industrial hygiene standards of 8-hour time-weighted-averages and ceiling levels are not protective. Prevention of the reaction by continued anti-asthma therapy offers a potential, though nonideal approach. The long-term cost is considerable, therapy may mask the occurrence of chronic effects, and therapy compliance may be poor during asymptomatic periods. Once sensitized, the worker must essentially avoid exposure.

RESEARCH NEEDS

Basic Research

Research efforts are needed to establish the allergic, irritant, or pharmacologic pathogenesis of occupational asthma. Mechanisms involved in the production of late or delayed onset occupational asthma also require elucidation. Additionally, the role of contaminating pollens, mold spores, and other "natural" aeroallergens in organic dusts needs to be clarified in many situations.

Epidemiologic Studies

Considerably more information should be obtained on the prevalence of occupational asthma.

ma in many industries. Data on the fate of the occupational asthmatic after ceasing exposure is also needed. Epidemiologic studies should seek to determine not only prevalences of sensitization but the relationship between dose received and the occurrence of sensitization. This can only be achieved by prospective studies with excellent follow-up.

Antigen Characterization

Research needs to be performed in order to characterize and partially purify the natural antigens involved in the production of occupational asthma. Research is also needed to develop suitable preparations for skin tests and *in vitro* tests for circulating IgE antibodies in asthma due to synthetic agents. Only by such research will satisfactory antigens for skin tests and RAST and similar assays be obtained.

Determination of Predisposing Factors

The many predisposing factors that might potentially lead to the development of occupational asthma need to be characterized. These include the presence of pre-existing irritable airways (as defined by methacholine challenge) and the atopic status of the individual (as defined by history and skin reactivity). Such information could be valuable in pre-employment screening designed to reduce the number of high risk individuals.

Education

Medical personnel associated with industry and unions should be made aware of occupational asthma and have both appropriate knowledge and suitable equipment for diagnostic use. Some research into means by which paramedical personnel and unions can be educated in this regard would be desirable.

Centers for Occupational Asthma

It is unlikely that research in the area of occupational asthma caused by so many agents can be carried out in existing small, ill-equipped centers. Thus the support of existing and the creation of new occupational lung disease centers in industrial areas throughout the country would serve as focal points for achieving broad research objectives. The overall goal of these centers should be to apply and adapt the efforts of research development as part of routine medical standards of practice in industry.

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SECTION IV
HYPERSENSITIVITY

HYPERSENSITIVITY PNEUMONITIS

Jordan Fink

INTRODUCTION AND DEFINITION

Hypersensitivity pneumonitis comprises a group of allergic lung diseases resulting from sensitization and recurrent exposure to inhaled organic dusts. The disease is a diffuse, predominantly mononuclear inflammation of the lung parenchyma, particularly the terminal bronchioles and alveoli. The inflammation often organizes into granulomas and may progress to fibrosis. A wide variety of dusts can cause the disease. These include: moldy fodder in farmer's lung; moldy sugar cane in bagassosis; bird droppings or other avian proteins in bird handler's lung; and mold spores in maple bark stripper's disease. Most individuals who develop hypersensitivity pneumonitis are exposed through their occupation. However, recent information has indicated that sensitizing organisms can also contaminate and be dispersed through forced air heating, humidification, or air conditioning systems, causing pulmonary disease in home and office occupants.*

No single clinical feature or laboratory test is diagnostic of the disease. Rather, the diagnosis is made from a combination of characteristic symptoms, physical findings, x-ray abnormalities, pulmonary function and immunologic tests. The demonstration of precipitating antibodies to a suspected inhaled antigen is particularly helpful. Occasionally, lung biopsy or inhalation challenge is needed. The diagnosis should be suspected in patients exposed to one of the offending antigens who have either repeated bouts of influenza-like pneumonitis or active interstitial lung disease. Although clinical and laboratory abnormalities tend to disappear when the offending dust is avoided, continued exposure may result in irreversible pulmonary damage. The allergic mechanisms and pathogenesis responsible for the development of this group of diseases are incompletely understood. Most in-

*See Kay Kreiss, M.D., *Building-Associated Epidemics*

dividuals exposed to an incriminated dust fail to develop disease. A number of the interstitial lung diseases of unknown etiology bear clinical and pathological similarities to hypersensitivity pneumonitis.

Certain types of hypersensitivity pneumonitis may be of particular importance. Maple bark stripper's disease, for example, is a hypersensitivity pneumonitis essentially eliminated by recognizing the conditions necessary for its development. Hypersensitivity secondary to contaminated forced air and humidification systems is potentially of great practical importance, considering the widespread use of these systems. Allergic bronchopulmonary aspergillosis is typified by the presence of bronchial asthma and eosinophilia, findings not common in hypersensitivity pneumonitis. However, the presence of precipitins to *Aspergillus* organisms (which colonize the airways in this disease) suggests a possible pathogenetic overlap with hypersensitivity pneumonitis and emphasizes the diverse ability of lung response to inhaled antigens.

LIST OF CAUSATIVE AGENTS

Hypersensitivity pneumonitis may occur following the inhalation and subsequent sensitization of antigens in a wide variety of organic materials. Offending agents may be bacterial (thermophilic actinomycetes), fungal (*Alternaria*, *Aspergillus*), serum proteins (avian proteins), chemical (anhydrides), or yet undefined (coffee dust). See a list of such agents on the next page.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

This is generally covered in the list of causative agents and is as varied as the variety of organic dusts which can cause hypersensitivity pneumonitis. The major occupations and industries associated with hypersensitivity pneumonitis are those in which moldy vegetable compost is handled—which by its very nature is contami-

Agent	Disease	Exposure
Definite Causative Agents		
<i>Thermophilic actinomycetes</i>		
Micropolyspora faeni	Farmer's lung	Moldy compost
Thermoactinomyces vulgaris	Mushroom worker's lung	
Thermoactinomyces viridis		
Thermoactinomyces sacharii	Bagassosis	Moldy sugar cane
Thermoactinomyces candidus	Ventilation pneumonitis	Contaminated forced air system
<i>Fungi</i>		
Cryptostroma corticale	Maple bark stripper's disease	Moldy maple bark
Aspergillus clavatus	Malt worker's lung	Moldy malt
Penicillium frequentans	Suberosis	Moldy work dust
Penicillium caseii	Cheese worker's lung	Cheese mold
Alternaria sp.	Woodworker's lung	Moldy wood chips
Pullularia sp.	Sequoiosis	Moldy redwood dust
Mucor sp.	Paprika splitter's lung	Paprika dust
<i>Arthropods</i>		
Sitophilus granarius	Wheat weevil disease	Infested wheat
<i>Animal Proteins</i>		
Avian proteins	Bird breeder's lung	Avian droppings
<i>Chemicals</i>		
Phthalic anhydride	Epoxy resin worker's lung	Epoxy resin
Toluene diisocyanate	Porcelain refinisher's lung	Paint catalyst
Probable Causative Agents		
Amoeba	Ventilation pneumonitis	Contaminated systems
Various fungi		
B. subtilis	Enzyme worker's lung	Detergent enzymes
Hair dust	Furrier's lung	Animal proteins
Coffee dust	Coffee worker's lung	?
Trimellitic anhydride	TMA disease	Trimellitic anhydride
Possible Causative Agents		
Altered humidifier water	Humidifier lung	Humidifier water
Various saprophytic fungi	Hypersensitivity pneumonitis	Contaminated environments

nated with thermophilic actinomycetes. Thus farmers (11)(14), sugar cane workers (10), and mushroom compost handlers (9) are exposed, as are individuals living or working in environments with ventilation systems contaminated with these organisms (5)(26).

Industries in which raw wood products are handled are prone to the development of hypersensitivity pneumonitis. There are reported prevalences in suberosis (cork) (4), sequoiosis (redwood)(13), maple bark (20), and wood pulp (57). Individuals involved in bird handling (pigeon racers, pigeon showers, budgerigar raisers) develop disease as a result of the inhalation of proteins from droppings, dander, saliva, and urine (22)(30)(49)(51).

The disease had also been described in chemical manufacturing and processing, especially when isocyanates and anhydrides are used (28)(56). Such areas include paint spraying and epoxy manufacture.

Other minor industries in which hypersensitivity pneumonitis may occur are variable and have little in common. As new areas of exposure and subsequent diseases are described, it has become apparent that a broad variety of inhalant organic dusts is capable of inducing hypersensitivity pneumonitis.

EPIDEMIOLOGY

Statistical reports of respiratory disease incidence do not commonly categorize hypersensitivity pneumonitis because the disorder is not yet widely recognized. Patients with this disease may be categorized under inhalation diseases, interstitial diseases, or occupational airway diseases (see "Estimate of Population at Risk and Prevalence of Disease"). The scant information regarding numbers at risk and estimates of numbers with diseases are depicted in Table IV-I (48).

There is little information available regarding a relationship between antigens, exposure, and disease. In a given population, similarly exposed to a potential sensitizing inhalational agent, the number of individuals with detectable disease has ranged from 3% to 15% (12)(45). Yet up to 50% of exposed but asymptomatic individuals in similar environments have detectable humoral or cellular immune responses to the antigen without clinical evidence of disease. Thus, some other unknown factor(s) is important in

the genesis of hypersensitivity pneumonitis. These may include:

1. **Genetic factors** — Recent evidence has demonstrated that pigeon breeder's disease is not associated with genetic immunologic responsiveness as determined by HLA typing of ill and well pigeon breeders (54). Other evidence has suggested that farmer's lung or pigeon breeder's disease may be under genetic control with an increased frequency of the HLA haplotype in ill individuals (1) (31). Additional studies are necessary to confirm this.
2. **Infection**—Recent evidence, using animal models of hypersensitivity pneumonitis, suggests that some inflammatory event must occur in the lung—in addition to recurrent antigen inhalation exposure—for disease to develop. Animals chronically exposed to pigeon antigens demonstrated an immune response, but no pulmonary inflammation was evident until an agent such as BCG or carageenan was given (46). Such agents, including infectious organisms, may stimulate the immune response by adjuvant action or by enhancement of antigen absorption through inflamed mucosa.
3. **Toxic factors**—The induction, progression, and severity of hypersensitivity pneumonitis may be related to a variety of toxic exposures. Possible toxicants include tobacco smoke, air pollution, and industrial exposures. A recent study has linked the occurrence of pigeon breeder's disease with the use of hexachlorobenzene as a disinfectant in pigeon lofts (1). The factors may enhance absorption of antigens as a result of pulmonary inflammation. They may also increase local immune responses or may act systemically as adjuvants.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

Hypersensitivity pneumonitis is not categorized in statistical reports of respiratory disease incidence. Because of its clinical presentation and pathophysiology, this disease may be classified with inhalation diseases, or even dis-

Table IV-1
AT RISK DATA ON SOME OF THE HYPERSENSITIVITY PNEUMONITIDES

Disease	Groups at Potential Risk	Numbers Potentially at Risk	Numbers with Disease
Farmer's Lung	At least, all dairy farmers At most, all farmers who store foodstuffs, doffer, or fibre	260,000 dairy farms Approximately 3 individuals per farm Maximum estimate 2.8 million workers	Unknown
Bagassosis	Persons who inhale bagasse dust—the residue of sugar cane. Recently, residue is burned, decreasing exposure.	Less than 5,000 persons	Unknown, though handling practices may have decreased exposure
Maple Bark Stripper's Disease	Persons who strip maple bark and are exposed to mold spores beneath the bark	Unknown	No new cases since log handling processes have been changed
Mushroom Worker's Disease	Persons who clean out mushroom bed houses	575 mushroom growers with 5,000—6,000 harvesters. The clean-out crews are a small percent of workers.	Unknown
Malt Worker's Lung	Workers in malting houses	1,800 persons in malt industry	Unknown
Pigeon Breeder's Disease	Breeders of pigeons for display or racing	75,000 to 100,000 breeders in the U.S.	Estimated to be from 6% to 15% of handlers
Isocyanate Disease	Paint sprayers Foam insulators	3,000 (hexamethylene) 6,000 (toluenc)	Most have asthma; hypersensitivity pneumonitis reported but rare
Phthalic Anhydride Lung Disease	Workers in epoxy resin, plasticizer manufacture	54,000	Unknown
Trimellitic Anhydride Lung Disease	Workers in plasticizer, surface coating manufacture	11,000	Unknown

Source: Mushkin, S. (48)

eases of the airways. Data are available on a few specific forms—especially farmer's lung—which have been studied in England and the United States. Even this information is sketchy because closed populations of farmers have seldom been studied; and while some prevalence data are available, little or no incidence data have been published.

Grant and associates in a study of 655 farm workers in Scotland, found the prevalence of *farmer's lung* to range from 2.3% to 8.6% in three different counties (34). Staines and co-workers, in another British study, estimated the prevalence of farmer's lung in two communities to range from 0.5% to 1% of the farm population (61). A more recent study of 93 farmers by Morgan and co-workers, in an area endemic for farmer's lung, showed that 9 (9.6%) had typical clinical histories of farmer's lung (47).

A recent U.S. study surveyed 471 persons associated with farming or dairy production (42). A history typical of farmer's lung syndrome was given by 14 (3.9%) of the population. The prevalence of farmer's lung in this community located in western Wyoming was comparable to the British and Scottish studies. There is little doubt that farmer's lung is an important occupational illness in farmers in this country, but the diagnosis may be frequently overlooked due to lack of patient and/or physician awareness. Smyth and co-workers found that less than 45% of patients with farmer's lung were diagnosed during the first year of their illness.

Recently 1,045 dairy farmers in central Wisconsin were surveyed for precipitins to a panel of antigens including thermophilic actinomycetes, aspergillus, and pigeon serum (43). Eight and one-half percent of the group had precipitating antibodies to one or more of the thermophilic actinomycetes while 0.4% had precipitins to one of the aspergilli. All of the individuals with precipitins were further evaluated. Thirty-six percent had a positive history of farmer's lung; 10% had a questionable history. Based on these findings, there exists a potential development of approximately 32 cases of farmer's lung per 1,000 in the dairy farmer population. This would result in 4,800 cases in the State of Wisconsin alone, a figure far exceeding the frequency of many other diseases. Such a high estimated prevalence is particularly alarming because these patients are at risk of developing chronic irreversible lung damage.

Estimates of the socioeconomic impact of farmer's lung are difficult to make. If the definitive treatment is to remove the farmer from his environment, the consequences are far reaching. The average dairy farmer at age 45 knows no other occupation. His farm—which is his home, as well as his place of business—often represents a considerable investment which may not be easily redeemable. Furthermore, farm wives seldom have outside employment and are generally not prepared to become part of an outside work force. Thus, the impact of such a situation on the family is apparent.

Changing farm practices could produce an environment relatively free of exposure to thermophilic actinomycetes. However, sufficient information is not currently available to determine the cost and effectiveness of the changes. There have been isolated instances where the farm environment and practices have been altered, but at a prohibitive cost of \$50,000 to \$100,000 (Wenzel, F., personal communication).

Of the over 600 cases of *bagassosis* referred to in the literature, approximately 500 have been detected in Louisiana. However, the disease is of worldwide distribution and occurs wherever sugar cane is processed. Cases have been reported from Louisiana, Texas, Missouri, Illinois, Puerto Rico, India, Cuba, Italy, England, and Peru (49). Several cases have been seen in non-occupationally exposed individuals such as persons using the material as a garden mulch; housewives residing in homes several miles downwind from sugar cane fields and processing areas; and employees working in air conditioned offices at or near sugar cane processing areas.

Pigeon breeder's disease has been estimated to occur in 6% to 15% of individuals who raise pigeons for a hobby (12)(29). There are approximately 75,000 breeders in the United States; therefore, if the estimated prevalence is correct, up to 10,000 of these individuals could develop irreversible lung damage.

Studies of several office worker populations exposed to contaminated air cooling systems have demonstrated a prevalence of hypersensitivity pneumonitis, 15% in one such outbreak (5) and less than 1% in another (3).

Thus, although specific prevalence and incidence data are not available for each type of hypersensitivity pneumonitis, it is known that the disease represents a serious health problem in many occupations. It is also believed to occur

more frequently in home and office environments than has been recognized (23).

PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

The lung is a unique organ in that it is presented with an extremely large number and variety of potential antigens. Important antigenic agents present in organic dusts are derived from fungal, bacterial, or serum protein sources. Because of the small particle size of these dusts (usually less than 5 μm), large quantities of antigenic material can be deposited at the alveolar level as well as in the airways. Under certain circumstances, this antigenic challenge can result in an immunologic response producing reactions in the airways and lung parenchyma. The clinical response to this challenge depends on the person's immunologic reactivity, i.e., atopic or non-atopic, the nature of the dust, the size of the particles, and the intensity of the exposure (particularly whether it is regular or intermittent)(49). The list of causative agents lists the various hypersensitivity pneumonitides and includes the type of exposure and the specific causative agent when it is known.

Pathology

Pathologic variation depends more on the timing of the antigen exposure than on the character of the offending antigen, since pathologic events are similar during the disease course for the different clinical entities (farmer's lung, bird fancier's lung, mushroom worker's lung, etc.). The intensity of any acute inflammatory event appears to vary with the dose of the specific antigen delivered to the lung and the interval between acute exposure and past episodes.

The lung morphology during acute clinical episodes is that of an acute granulomatous interstitial pneumonitis (Figure IV-1). The alveolar spaces contain numerous macrophages and foreign body giant cells, as well as neutrophils, and a modest number of eosinophils. The macrophages frequently contain some stainable neutral fat. The alveolar walls are often thickened, edematous, and infiltrated by neutrophils, a few eosinophils, and macrophages. As the chronicity of the process develops, the inflammatory exudate within the interstitial tissue has more of a plasmacytic or lymphocytic character. The inflammatory exudate is paucicellular in the earli-

est stages; some fibrinous exudate may also precede the inflammatory cells. The granulomatous lesions consist of dense collections of plump epithelioid cells arranged in palisaded fashion, and often surround zones of liquefaction necrosis in which some necrotic tissue debris and a few inflammatory cells remain. Bronchioles are often involved and demonstrate a necrotizing process which destroys portions of their mural structure and occludes the bronchiolar lumen with macrophages, inflammatory cells, and tissue debris. The bronchiolar epithelium may be destroyed and replaced by flat, regenerating epithelium. The involved adjacent alveoli are lined by hypertrophied cuboidal epithelial cells (59).

As the process unfolds, its course may be influenced by several factors: the degree of sensitization to the offending, specific antigenic material; the amount of antigen presented in the current episode; and the number and timing of any repeat exposures to the same antigen. If the degree of sensitivity is minimal, or the antigen dose encountered during the inciting episode small and the encounter not repeated, the inflammatory episode may resolve with little or no residual tissue changes. If the inflammatory process persists—either due to persistence of the chronic reaction or to the periodic recurrence of acute exacerbations—the lung will suffer insidious or episodically overt continued tissue destruction. Noncaseating granulomas may then be seen with greater frequency. The inflammatory exudate within alveolar spaces and bronchiolar lumenina may become invaded with fibroblastic cells and will contain distinctive Masson bodies which are evidence of organization of alveolar exudate. The chronic inflammatory exudate within the interstitial and alveolar septa will increase in amount; will be characterized by a greater number of plasma cells; and will become thickened by fibroblastic invasion and hypertrophied alveolar epithelial cells (19).

After a prolonged period of repeated acute insults and persistent chronic inflammation, diffuse interstitial fibrosis or honeycomb lung may develop. Within the fibrosis, inflammation may persist in the interstitial and alveolar septa which will have been thickened by mature collagenous connective tissue and some residual chronic inflammatory cells. Noncaseating granulomas are infrequent or absent and may be replaced by collagen or hyalinized tissue. The alveolar spaces are modestly enlarged and the walls thickened



Figure IV-1. Photomicrograph of lung biopsy from 23-year-old woman with hypersensitivity pneumonitis due to contamination of the home humidification system. Sarcoid like granuloma formation and diffuse lymphocytic infiltration is evident.

by fibrosis and alveolar cell hyperplasia. Intra-alveolar organizing Masson bodies are seen. Small muscular arteries are thickened and sclerotic. In honeycomb lung, a similar residual chronic inflammatory process may be present in the interstitial and intra alveolar spaces, and the airspaces are enlarged and cyst-like—reaching a dimension of 0.5 cm to 1.0 cm. The walls of these spaces are fibrotic; contain elements of hypertrophied smooth muscle, plasmacytes, and lymphocytes; and are frequently lined by hypertrophied bronchial epithelial cells. The muscular arteries and arterioles are markedly thickened (59).

The characteristic abnormality in acute tissue reaction is acute inflammation along with granulomas composed of plump epithelioid cells with necrosis and tissue destruction. The presence of large foamy macrophages has been most frequently observed in bird fancier's lung (37) (Figure IV-2).

While bronchioles may be involved with a

resulting obstructive organizing bronchiolitis, the lesion is clearly alveolar, inflammatory, and capable of tissue destruction. Since the involvement is usually focal and does not involve large amounts of lung tissue, the functional abnormalities observed may reflect alveolar wall involvement and, to a lesser degree, airways disease, which can produce a decrease in the diffusion capacity of the lung and slight compromise in tests of ventilation. In later stages, the lesions show evidence of tissue loss and some form of fibrosis or scarring.

Pathogenesis and Immunopathology

The potential antigens for hypersensitivity pneumonitis are almost infinite when one considers the number and varieties of substances inhaled into the lungs during a lifetime. A complex relationship must exist between the type and dose of inhaled antigen, the removal mechanisms, and the lung's defense systems.

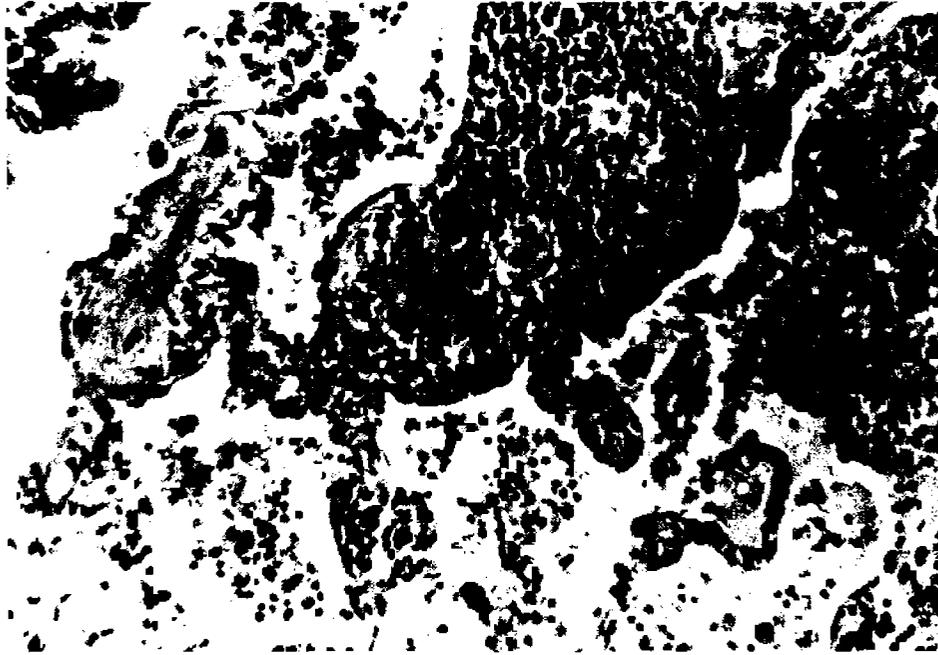


Figure IV-2. Photomicrograph of lung biopsy from 45-year-old pigeon breeder with recurrent acute episodes. Lymphocytic interstitial infiltration, foamy macrophages, and granuloma formation are evident.



Figure IV-3. Immunodiffusion in agar of patient's serum (center wells) against pigeon antigens (peripheral wells) resulting in precipitin reaction.

The immunologic hallmark of hypersensitivity pneumonitis is the presence of serum precipitins to the inhaled antigen (49) (Figure IV-3). Precipitins are present in over 90% of patients with clinical disease and are usually of the IgG class of immunoglobulins. In comparison, as many as 50% of individuals with appropriate exposure to the antigen also have precipitins, but are asymptomatic (24). These percentages probably represent minimal estimates since the detection accuracy depends on the sensitivity of methods employed and the number and diversity of antigenic preparations available for testing. There is considerable overlap in the titers of symptomatic and asymptomatic individuals, therefore, the titer itself is neither diagnostic nor prognostic.

With the exception of patients who have an asthmatic response to an inhaled antigen, the role of serum antibodies is not clear and may represent a natural immune response to an inhaled antigen. The elevated specific IgE antibody is present only in atopic individuals who have the immediate airways obstructive reaction characteristic of asthma.

The immunologic events responsible for the physiologic and anatomic abnormalities in acute and chronic hypersensitivity pneumonitis are not well understood. There is evidence both for and against an immune complex role. The presence of IgG precipitating antibodies in the majority of patients, and the temporal relationship between antigenic exposure and the onset of acute illness (4-10 hours) are compatible with an immune complex and complement-mediated (Arthus-type) immunologic reaction. In addition, lung biopsies obtained during acute reactions show infiltration of the alveolar walls chiefly with lymphocytes and plasma cells while polymorphonuclear leukocytes and eosinophils occur only in modest numbers. Within the alveoli are foamy macrophages that contain C3 (67). In contrast to the findings in experimental Arthus-type reactions, there is no direct relationship between the antibody titer and the severity of the acute reaction in patients with hypersensitivity pneumonitis. In some patients the precipitin titers may fall below the level of detection, yet clinical sensitivity persists (49). Patients with chronic hypersensitivity pneumonitis may have low antibody levels in their sera although their broncho-alveolar lavage fluids contain increased concentrations of IgG, and in many instances, increased titers of anti-

body against the presumed etiologic agent (52). However, attempts to demonstrate immune complexes within alveolar lesions have been unsuccessful.

Additional evidence that IgG mediated reactions are not solely responsible for hypersensitivity pneumonitis comes from animal studies. In guinea pigs sensitized so that they produced antibodies but not cellular immunity, inhalation challenges produced a hemorrhagic alveolitis that was not morphologically compatible with farmer's lung (53). Moreover, it has not been possible to passively transfer the disease to monkeys with antibody-containing serum (36). Thus, even though skin testing of persons with pigeon breeder's disease (with pigeon serum) produces Arthus-like responses at 4-6 hours, current evidence suggests that this reaction, like the serum precipitins, is a consequence of antigenic exposure. Its relationship to the pathogenesis of the disease is unclear. Similar studies are not currently feasible in exposed farmers because there are no generally available soluble extracts of thermophilic actinomycetes suitable for skin testing for farmer's lung. Additional evidence for the participation of humoral factors in hypersensitivity pneumonitis includes demonstrations that the alternate pathway of complement fixation may be activated by spores of thermophilic actinomycetes (16). This pathway may play a direct role in the genesis of the inflammatory response within the lung or may interact with the circulating antibody and immune complexes to induce lesions.

Other evidence suggests a role for cell-mediated immune responses in the pathogenesis of hypersensitivity pneumonitis. Biopsies show lymphoid cell infiltrations and granuloma formation suggesting this type of immune response. Lymphocytes from patients with pigeon breeder's disease or farmer's lung may produce a macrophage migration inhibition factor when exposed to the appropriate antigens *in vitro*, and blood lymphocytes from symptomatic pigeon breeders may respond to pigeon serum antigens with increased thymidine incorporation (lymphocyte transformation) (35)(45). Analyses of peripheral lymphocyte subpopulations in patients with hypersensitivity pneumonitis have demonstrated reduced circulating T-cells in those with active disease (32), and analyses of lavage lymphocyte subpopulations of patients with chronic hyper-

sensitivity pneumonitis have demonstrated a significant increase in T-cells when compared with blood (52).

Animal data are also compatible with a cell-mediated reaction in hypersensitivity pneumonitis. Guinea pigs with delayed hypersensitivity to protein antigens respond to inhalation challenge with the production of interstitial infiltrations that resemble the acute disease in humans (53). Similar lesions have been induced in monkeys by passive transfer of cells from donors sensitized to pigeon serum (36). Antibodies and complement were not detectable in the pulmonary lesions of recipients. Although these observations strongly suggest cell-mediated immunity plays a role in the pathogenesis of hypersensitivity pneumonitis, it does not exclude the possibility that a combination of immune complex and complement along with cell-mediated reactions are necessary for production of clinical hypersensitivity pneumonitis in exposed individuals.

Most patients with hypersensitivity pneumonitis have demonstrable precipitating antibodies and cellular immune reactions to an offending antigen. Thus, it is likely that several types of immune reactions are important in the pathogenesis of the disease.

Pathophysiology

The nature and extent of the physiologic events occurring in hypersensitivity pneumonitis depend primarily on the clinical form of the disease.

Acute Form

The acute form of hypersensitivity pneumonitis is characterized clinically by chills, fever, cough, breathlessness without wheezing, and malaise 4-10 hours after antigen exposure (30). There is some correlation between the severity of the acute episode and magnitude of the antigenic challenge; however, immunologic responsiveness also influences the severity of an attack. In general, an acute attack subsides after 18 to 24 hours.

The classic response to antigen exposure results in maximum changes 8 to 10 hours after exposure (55). Changes are primarily restrictive with a decrease in FVC, FEV₁, and TLC. There is little change in flow rates, but small airways obstruction can be demonstrated. There is a decrease in static compliance, and dynamic compliance becomes frequency dependent. Changes

in the small airways result in nonuniform ventilation distribution and, in turn, disturbance in ventilation-perfusion relationships. Hypoxemia and impaired diffusing capacity are manifestations of this mismatching (58)(65). Hypoxemia may also be caused by redistribution of blood flow with resulting ventilation-perfusion inequality or be secondary to intrapulmonary shunting of blood. The pulmonary circulatory response is unclear in the acute form of hypersensitivity pneumonitis.

Several other patterns of response are seen. The late reaction can be preceded by an immediate asthmatic reaction with decrease in FEV₁ and expiratory flow rates. These changes resolve in 1 to 2 hours.

In atopic subjects, an acute asthmatic response (with wheezing and evidence of airflow obstruction on standard testing) may occur within minutes after antigen inhalation (49)(55). This attack may subside with or without treatment, but 4-10 hours later the response will still occur. Patients with bronchopulmonary aspergillosis will also have this dual response. By contrast, however, their response is also characterized by an obstructive pattern on standard physiology testing. Less commonly, a repetitive asthmatic reaction occurs, resulting in an immediate obstructive type response with resolution and then a series of asthmatic episodes of decreasing intensity at 8 to 12 hour intervals for several days. In addition, there can be an immediate asthmatic reaction which persists for 4 to 6 hours (49).

In the majority of patients with the acute disease form—particularly with exposure avoidance—pulmonary function returns to normal within a few weeks to months. Even with repeated acute attacks, if the exposure is not intense or frequent, physiologic function may remain normal between exposures.

Subacute Form

A small number of patients show a more insidious disease form resembling a progressive chronic bronchitis with productive cough, dyspnea, easy fatigue, and weight loss (24)(30)(49). Both restrictive and obstructive defects in pulmonary function can be observed; the former, however, predominate along with a decrease in static lung compliance and diffusing capacity. Hypoxemia, although only mild at rest, may show a substantial worsening with exercise. Long-term

avoidance of exposure and administration of corticosteroids usually result in resolution of these functional abnormalities.

Chronic Form

Prolonged and intense exposure to an organic dust causing hypersensitivity pneumonitis can lead to the gradual development of disabling respiratory symptoms with irreversible physiologic changes (24)(49). Pulmonary fibrosis is the predominant finding, particularly in farmer's lung or in patients with chronic low-level exposure to antigens (6). These patients have progressive restrictive impairment, a diffusion defect, hypoxemia, and decreased lung compliance. Pulmonary fibrosis may progress, even without further exposure and despite corticosteroid therapy, eventually resulting in respiratory failure. A few patients with the chronic form of the disease have also shown signs and symptoms of obstructive disease (58). Physiologic studies show diminished flow rates, hyperinflation with markedly elevated residual volume, decreased diffusing capacity, and a loss of pulmonary elastic recoil pressure suggestive of emphysema. Biopsy specimens in these cases have revealed an obstructive bronchiolitis with distal destruction of alveoli. Avoidance of exposure (even for prolonged periods), corticosteroids, and bronchodilator therapy afford only minimal improvement; the disease tends to be progressive (30).

CLINICAL DESCRIPTION

Symptoms

The onset may be acute or insidious (24) (49). When exposure is relatively heavy but intermittent, symptoms begin abruptly 4 to 6 hours later. Chills, fever of 101 to 104 degrees (38.3° to 40°C), malaise, dry cough, dyspnea, and easy fatigability may persist for several weeks. With repeated exposure, weight loss of 10 to 20 lbs. is usual. Involvement of the airways is exceptional, and most patients do not develop both asthma and hypersensitivity pneumonitis.

When exposure is (relatively) less intense but more continuous, chills and fever may not occur. Exertional dyspnea, cough with scanty mucopurulent sputum, easy fatigue, and weight loss are usual symptoms. An acute episode is rare, unless exposure is exceptionally intense.

In the chronic form of the disease, the symptoms are mainly respiratory and consist of

progressive shortness of breath, leading to pulmonary disability. There may be associated anorexia and weight loss with mucopurulent sputum, but acute episodes do not occur (30).

Signs

Inspiratory rales, resembling crackling cellophane, can be heard throughout the lungs but are loudest at the bases. The rales may be heard only at the peak of an acute illness or may persist for weeks or months. Wheezing or prolonged expiration occur occasionally in patients allergic to birds and a few other antigens, but does not occur with exposure to thermophilic actinomycetes. Ankle edema and enlargement of the liver indicate complicating right-sided heart failure.

Other aspects of the physical examination serve mainly to exclude other diagnoses. Peripheral lymphadenopathy does not occur, and hilar adenopathy is unusual. Complicating arthritis or skin rashes are not observed.

Natural History and Prognosis

With the exception of farmer's lung, the number of patients with hypersensitivity pneumonitis seen by one group of investigators is small. This has made large-scale longitudinal studies difficult and consequently the natural history of this disease is poorly understood. In addition, only a few individuals will develop disease after antigen exposure. As a result, the problem may not be recognized in a given case. Often there will be voluntary avoidance of exposure by the affected person even though the exact cause and effect relationship is not understood.

The clinical course of this disease depends to a large extent on the intensity and duration of exposure. In general, a brief exposure, even though intense, will result in an acute reaction in the sensitive individual followed in several days to weeks by complete resolution of symptoms and return of pulmonary function to normal, or near normal, with avoidance of exposure. Recovery can be accelerated by the use of corticosteroids. However, with repeated acute exposure, to an antigen or with chronic low-level exposure, progressive disabling respiratory symptoms with irreversible physiologic changes may result. This type of exposure has frequently been found in patients with farmer's lung.

There is only limited data available on the long-term prognosis and physiologic abnor-

malities in the chronic phase of hypersensitivity pneumonitis. A study of 50 patients with farmer's lung disease over an average period of 6 years showed a mortality rate of 10% (6). In this same group, 30% had persistent respiratory symptoms and physiologic abnormalities—with pulmonary fibrosis being the major problem. In an earlier retrospective study of 24 patients, 4 died during the period of observation after a 2 to 10 year duration of illness (19). Three of five patients who had lung biopsy in the acute stage and subsequently progressed to the chronic stage have been reported (59). A recent study of farmer's lung in Devon, England included 200 patients diagnosed between 1939 and 1971 (60). There were four deaths from farmer's lung, and severe disability was present in approximately one-third. Disability was commonly associated with restriction and reduced diffusing capacity and with airways obstruction in severe cases. Both face masks and steroids were utilized by many of the farmers included in this study.

In a review published in 1958 dealing with bagassosis, it was reported that 4 of 53 patients with the disease had died, representing a mortality rate of 7.5% (10). However, this figure was felt to be falsely high since many milder cases undoubtedly escaped medical attention. Several recent studies of acute bagassosis outbreaks (the follow-up usually performed within 12 subsequent months) showed that with exposure avoidance—even without corticosteroids—the restrictive impairment and abnormal diffusing capacity returned to normal (39)(65). In contrast, another study found similar functional changes during the course of the acute illness; but while chest x-rays returned to normal, the restrictive impairment and reduction in diffusing capacity, although improved, persisted even after 12 months of follow-up (50). Ten patients with pigeon breeder's disease followed with serial pulmonary function studies for 10 years have shown a variable pattern. Individuals who had normal function at the time they were first seen have tended to remain within normal limits despite occasional acute episodes. Patients who had either a restrictive impairment or, as in 2 cases, severe airways obstruction, were found to show only slight improvement and, in some cases, a more rapid deterioration in function than normally expected even in the absence of further pigeon exposure (Schlueter and Fink, personal observations). An-

other study with a shorter follow-up period reported a similar finding, particularly with regard to the diffusing capacity (15). A recent study of nine afflicted breeders showed complete recovery in four patients at 8 to 30 months after they had ceased being exposed to the antigen. The other five all had evidence of interstitial damage; three had progressive increase in the degree of airways obstruction and one had loss of elastic recoil. The patients were nonsmokers, and occult antigen exposure was ruled out because the precipitating antibody studies became negative (2). Neither the nature or degree of lung function abnormality nor the form of clinical presentation was related to the development of residual damage. The period of continued exposure after symptoms developed and the patient's age appeared to be the most important factors determining recovery of lung function.

It would appear that although the spectrum of response to antigen exposure in patients with hypersensitivity pneumonitis is broad, exposure avoidance results in complete resolution of abnormalities in most cases. Continued exposure, however, can lead to progressive and irreversible disease. When a substantial volume of lung tissue is involved and alveolar hypoxia is chronic, pulmonary hypertension develops. Chronic and sustained pulmonary hypertension will lead to right ventricular enlargement and ultimately to right ventricular failure. Respiratory failure as a result of extensive destruction and fibrosis of lung tissue may be seen in the end stages of chronic, progressive lung disease.

Appropriate Laboratory Investigations

Pulmonary Function Studies

A number of pulmonary function abnormality patterns can occur depending on the clinical form of hypersensitivity pneumonitis (49)(55).

During acute episodes the most common response occurs from 4 to 6 hours after exposure to the offending antigen. There is a decrease in forced vital capacity (FVC) and one-second forced expiratory volume (FEV₁), with a constant ratio between these two parameters. There is little change in expiratory flow rates. A decrease in compliance indicating increased lung stiffness and a fall in diffusion capacity also occurs during acute episodes. Determination of arterial blood gases usually demonstrates hypoxemia

which is accentuated by exercise. Closing volumes may also increase and maximal mid-expiratory flow rates decrease. As the attack subsides, these abnormalities resolve. If there is parenchymal damage, however, volume and flow abnormalities, as well as hypercapnia, may be found during asymptomatic phases.

Some individuals with hypersensitivity pneumonitis exhibit a two-stage reaction. Immediately after exposure, an asthmatic response occurs with a decrease in forced vital capacity, forced expiratory flow volume and expiratory flow rates. This response is followed by the late 4 to 6 hour response described above. Controlled laboratory challenge studies have demonstrated that the immediate pulmonary function response can be reversed with bronchodilators; the late response is resistant to these drugs. Pretreatment with corticosteroids blocks the late response, and cromolyn may block both responses. The findings suggest that different mechanisms may be involved in the two types of responses.

In patients with the more chronic forms of hypersensitivity pneumonitis, less reversible pulmonary function abnormalities may be detected. In the subacute form, a more persistent restrictive impairment and diffusion defect may be demonstrated during exposure and even for some time after cessation of contact with the antigen (58).

The most marked physiologic alterations have been found in patients with the chronic form of hypersensitivity pneumonitis—readily studied in individuals with pigeon breeder's disease (30) or farmer's lung (6). A severe restrictive impairment with a moderate-to-marked diffusion defect has been shown to persist in some of these patients and may be physiologically correlated to the pulmonary fibrosis demonstrable on chest x-ray and lung biopsy.

Other individuals with chronic hypersensitivity pneumonitis may demonstrate poorly reversible and progressive obstructive disease with hyperinflation and elevation of residual volume. A loss of pulmonary elasticity with increased static compliance can be detected in these individuals (58). Some of this latter group may also have decreased diffusion capacity. These findings may correlate with biopsy evidence of obliterative bronchiolitis and emphysema (30).

Radiologic Studies

Chest x-ray studies of patients with hypersensitivity pneumonitis can be normal if recur-

rent episodes are infrequent. Usually, however, there are detectable, fine, sharp nodulations and reticulations with general coarsening of bronchovascular markings. During an acute attack, soft, patchy, ill-defined, diffuse parenchymal densities—which tend to coalesce—may be seen in both lung fields. Chronic or end stage disease may present as diffuse fibrosis with parenchymal contraction or even honeycombing (64) (Figures IV-4 and IV-5).

Immunologic Studies

The characteristic immunologic feature of hypersensitivity pneumonitis is the occurrence of serum precipitating antibodies against the specific organic dust antigen. Agar gel diffusion techniques with a suspect antigen and patient serum can be used to demonstrate antibodies in almost all ill individuals. However, these tests must be evaluated in light of clinical findings since up to 50% of similarly exposed but asymptomatic individuals may also have moderate to high titers of serum precipitating antibodies. The antibodies in symptomatic and asymptomatic individuals belong largely to the IgG class of immunoglobulins, but IgA and IgM antibodies have also been detected in these sera.

Cell-mediated immunity to organic dust antigens has recently been detected in the peripheral lymphocytes of patients with hypersensitivity pneumonitis. While these tests may be more specific for hypersensitivity pneumonitis, and may more readily discriminate between ill and well individuals than do tests for humoral immunity, they are not generally available.

Skin tests with bird sera and some of the mold antigens may evoke a dual phased skin reaction. A positive response consists of an immediate wheal-and-erythema reaction followed 3 to 8 hours later by an area of dermal and subcutaneous swelling several centimeters in diameter. Other antigens such as the thermophilic actinomycetes are not suitable for skin tests as they evoke a nonspecific constant inflammatory response in nearly everyone.

Blood Studies

A polymorphonuclear leukocytosis of up to 25,000/mm³ with a shift to young forms is the usual finding in the acute phase of hypersensitivity pneumonitis, but it resolves with recovery. Eosinophilia of up to 10% may be seen but is unusual. The leukocytosis is not evident between attacks.



Figure IV-4. Chest x-ray of 35-year-old pigeon breeder with recurrent acute episodes of hypersensitivity pneumonitis. Nodular interstitial infiltrates are prominent at the bases.

There is generalized elevation of immunoglobulin levels, except for IgE. Rheumatoid factor tests are often positive during periods of illness, but become negative after prolonged avoidance.

Diagnostic Challenge

Inhalation challenge testing may be carried out by exposing the patient to the suspect environment, or by cautious inhalation challenge with the suspect antigen in a pulmonary function laboratory. The technique may confirm the diagnosis by reproducing a typical acute attack with fever, rales, leukocytosis, and pulmonary function abnormalities occurring four to six hours after exposure.

Treatment

The major therapy for hypersensitivity pneumonitis is the same as for all allergic disorders once the offending antigen is known—avoidance. Since many of these disorders are occupational, and the antigen size is known, the use of

masks with filters capable of removing the antigen, appropriate ventilation of working areas, or as a last resort, changing of occupations may be necessary (24)(49).

In the acute or subacute forms of hypersensitivity pneumonitis, when avoidance cannot be quickly achieved, drug therapy can be instituted. Corticosteroids are the drug of choice and will abort and prevent the episodic illness. Antihistamines and bronchodilators have no effect. If the corticosteroids are administered while avoidance is practiced, reversibility of the clinical and laboratory abnormalities is usually possible. Immunotherapy, as used for treatment of atopic diseases such as asthma and allergic rhinitis, is contraindicated in hypersensitivity pneumonitis because of the possibility of immune complex vascular damage.

DIAGNOSTIC CRITERIA

The diagnosis of hypersensitivity pneumonitis is dependent on associating the pulmonary and/or systemic response of the patient with



Figure IV-5. Chest x-ray of 56-year-old farmer with severe pulmonary impairment as a result of chronic farmer's lung. Diffuse interstitial involvement is present.

the inhalation of a specific environmental dust. The disorder should be suspected in individuals with recurrent "flu"-like episodes, chronic unexplained cough, sputum and dyspnea, or in individuals with chronic progressive pulmonary impairment. The history may be important in differentiating hypersensitivity pneumonitis from other forms of interstitial pneumonitis in that it may bring out a temporal relationship between exposure (hobby or occupation) and symptoms. However, if the exposure is constant, the symptoms may be insidious and progressive and the diagnosis more obscure.

The physical examination is not specific for hypersensitivity pneumonitis. The acute attack is characterized by the presence of diffuse bibasilar rales indicative of an interstitial process. Fever and leukocytosis occur during the acute episode and these features disappear with recovery. This spontaneous recovery and subsequent recurrence should suggest an allergic phenomenon.

Pulmonary function abnormalities are not specific. An acute episode is associated with transient restriction, diffusion defects, and more persistent functional defects including high grade irreversible obstruction or severe restriction and diffusion impairment.

The chest x-ray features of hypersensitivity pneumonitis are variable, with findings ranging from no abnormality to diffuse interstitial fibrosis. The most common features are diffuse nodular infiltrates and coarse bronchovascular markings, which disappear with avoidance. Hilar adenopathy is rare.

The clinical features of hypersensitivity pneumonitis may be present in most other interstitial lung diseases such as chronic eosinophilic pneumonia, the collagen-vascular diseases, lymphogenous spread of carcinoma, desquamative pneumonitis, and sarcoid. The finding of extrapulmonary involvement (splenomegaly, lymphadenopathy) is rare in hypersensitivity pneumonitis. At times lung biopsy may be neces-

sary to confirm the diagnosis.

The most consistent feature of hypersensitivity pneumonitis is the presence of serum precipitating antibodies to an offending organic dust in affected individuals. However, these antibodies can also be detected in the serum of up to 50% of exposed but well individuals. Therefore, the finding of these antibodies must be evaluated in light of a patient's clinical features. Recent evidence has suggested that cellular immune responses to specific antigens may be more specific than humoral responses in the diagnosis of hypersensitivity pneumonitis. Additional studies are necessary to confirm these observations.

A suspected diagnosis may be confirmed by observation of the patients for clinical and pulmonary function changes following natural exposure to the environmental dust or following provocative challenge by controlled insufflation. Observation following removal of the individual from the suspect environment may also aid in confirming the diagnosis. These measures have been shown to be specific for the etiologic agent in hypersensitivity pneumonitis and are likely the key in confirming the diagnosis.

METHODS OF PREVENTION

The most effective control measure for abnormalities associated with hypersensitivity pneumonitis is removal of the affected worker from the occupational exposure—a step often quite disruptive to the individual involved. A more satisfactory approach would be prevention of the disease through the lowering of antigen levels in the work environment. In a few instances, such as in the lumbering industry, exposure of workers to potentially problematic dusts has been prevented by operational changes. For example, maple bark stripper's disease has been eliminated by altering handling of the logs (F.J. Wenzel, personal communication). The disease is caused by the inhalation of the spores of *Cryptostroma corticale*, a mold found growing beneath the bark of maple logs. The disease was first described in a group of bark peelers in northern Michigan in 1932 (63). The next report of the illness occurred in a paper mill in northern Wisconsin. At that site, out of 35 men tested, 5 had severe clinical disease, 9 had subclinical disease, and 4 others had serological evidence of exposure. The remaining 17 appeared normal (66).

High dust concentrations occurred in the

wood room, and it was shown that most of the dust material consisted of spores of *Cryptostroma corticale*. Clouds of spores could be seen each time an infected maple log entered the saw area. The spore counts were particularly high in the winter because of the poor ventilation of the wood room. To combat these conditions, changes were made including: eliminating the saw area by installing debarking drums; spraying the drums continuously with water containing a detergent; isolating the chippermen from the wood room with a glass positive-pressure room; and cautioning the workroom crew against spending excessive time in areas of high dust concentrations. These changes resulted in a dramatic fall in spore counts during the winter of 1964, and there have been no further cases of maple bark disease at the plant since that time.

Attempts to prevent bagassosis have been made by drying the material or by treatment with propionic acid to prevent growth of microorganisms (40). Bagassosis has also been reported to have been eliminated from a Louisiana paper mill by process changes (41). These involved both storage and processing modifications which retarded microbial growth and reduced the generation of organic dust.

Hypersensitivity pneumonitis due to the inhalation of microorganisms present in industrial air handling systems may also be amenable to engineering control. The microorganism reported to have been associated with this type of pneumonitis has varied presumably due to environmental conditions within the system. In an industrial context, contaminated humidifier water is most likely to cause problems. This type of pneumonitis may constitute a serious health problem occurring more frequently than is generally realized.

Where such preventive approaches are not possible or feasible, it would be helpful to be able to screen applicants for sensitivity to antigens and selectively prevent those susceptible from contacting the offending dusts. However, such testing is not currently available since factors (other than exposure) which lead to sensitization are not known.

Immediate, practical measures of hypersensitivity pneumonitis prevention and control include the education of individuals and industries at risk. Workers exposed to incriminated organic dusts must be made aware of potential hazards. Pertinent industries must be encouraged to

reduce sensitizing and challenging exposures. Industrial physicians, public health officials, primary care physicians, and consultants must be alerted to the importance of prevention as well as diagnosis and treatment of this group of diseases.

The limited, current control of hypersensitivity pneumonitis is primarily confined to manipulations of an afflicted individual's environment. Environmental factors have been clarified by studies of causative agents and their sources, and individual patients have benefited greatly by these studies. Of greater economic and epidemiological importance, however, will be predictive and preventive measures affecting whole environments and communities of workers which will result from an increased understanding of sensitizing events and host factors. Further research is required to establish knowledge necessary for the design of feasible preventive programs and the maintenance of a healthy, stable, work force in relevant environments.

RESEARCH NEEDS

The first research priority for hypersensitivity pneumonitis is pathogenetic cognizance. An almost infinite number of antigens are inhaled and enter pulmonary tissue, but only certain ones can apparently cause sensitization and disease—and only in certain exposed individuals. Factors and events essential for an inhaled antigen to induce disease need further investigation. Also essential is research into the roles of various peripheral and central humoral and cellular mechanisms—including immune complexes, specific immunoglobulin classes, and suppressor and helper T-cells.

A second priority should be the development of animal models to study a number of disease factors. These would include the immunopathogenesis, the conditions necessary for sensitization, and the evaluation of progressive damage to the lung. Animal models would also provide a means for screening antigens for their immunopathogenicity.

A third priority should be an intensive study of antigens known to cause disease. Immunochemical analysis of various antigens may determine possible common features between disparate organic dusts and may lead to the development of preventive or diagnostic tests. Studies are also needed to explore new antigens in the environment which may induce pulmonary dis-

ease. Such studies may require biochemical, microbiologic, and immunochemical techniques. Furthermore, antigen standardization investigations, utilizing reference dusts and human sera, are important.

Finally, it is necessary to determine the prevalence and natural history of these diseases, perhaps by a national cooperative study. Initial studies should be carried out in well defined populations such as farmers, malt workers, or pigeon breeders. Data collection should include quantitation of the environmental antigen load in order to correlate the level of exposure with the type of immune response.

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SECTION V
CHRONIC AIRWAYS OBSTRUCTION

CHRONIC BRONCHITIS AND EMPHYSEMA

Kaye H. Kilburn

DEFINITIONS

Chronic bronchitis is defined for epidemiological purposes by the presence of chronic or recurrent cough which occurs without localized bronchopulmonary disease, is productive of phlegm or sputum, and is present for at least three months of two sequential years. Its clinical definition adds a third qualifying criterion: dyspnea and/or airways obstruction. Chronic bronchitis data has been largely based on one research instrument—the Medical Research Council questionnaire, which defines the disease by cough and phlegm (72). The pathologic definition of bronchitis is descriptive and includes two elements: (a) hypertrophy and hyperplasia of bronchial mucous glands, together with goblet cell hyperplasia and squamous metaplasia of the surfaces of large and medium sized airways, and (b) goblet cell metaplasia of the small airways; i.e., airways without cartilaginous support, correlating with dyspnea and significant impairment of respiratory function.

Emphysema is characterized by abnormal, permanent enlargement of airspaces distal to terminal bronchioles, accompanied by destruction of their walls (20). Caution should be observed in attributing the absence of alveolar walls to destruction; such an absence could equally well reflect an inherent formative failure. Because emphysema is an anatomic diagnosis, a purist might insist the disease cannot be diagnosed before tissue is available. However, radiographic features together with increased lung volumes (total lung capacity being the crucial measurement; whereas increased vital capacity may provide the clue on screening examination) are currently utilized as acceptable criteria with which to distinguish the emphysema component in subjects with "chronic obstructive airways disease." Use of this and similar nonspecific phrases which avoid anatomical definitions by substituting

clinical or physiological criteria for grouping patients is a regressive step to be discouraged. The combined use of historical, physiological, and radiographic criteria permit recognition and diagnosis of chronic bronchitis (hypersecretion) alone; emphysema alone; or the two in conjunction. It is generally possible to assign a proportion of pulmonary disease or impairment to each so that it is not necessary or helpful to abdicate diagnostic precision. Prospective measurements of airways obstruction and lung volume in occupational groups, which would furnish interval decrements or increments, would yield data with which functional impairments could be specified; thereby, the progression rate and importance of exposure could be sorted out. Longitudinal studies (which measure decrements with time in the same individuals) are clearly more sensitive for abnormality than is comparison to a predicted value (which is a measurement limitation of cross-sectional studies). Because these terms have occasionally been used in the literature without sufficient information provided to group patients into diagnostic classifications, it may be necessary to refer to information collected under a broad designation such as chronic obstructive airways or lung disease. In those cases, the definition of chronic airways obstruction is a reduction in flow from the lungs during a forced expiration from maximum inspiration. Asthma is characterized by significant reversibility of this obstruction either spontaneously or due to drugs.

LIST OF CAUSATIVE AGENTS

Because the etiology of chronic bronchitis is still unknown and there is no satisfactory model, causative agents must be considered as tentative groupings based upon clinical and epidemiological data. The pathogenetic role of viruses and explicit bacteria lacks distinct cause-

Table V-1
LIST OF CAUSATIVE AGENTS

	Definite	Probable	Possible
Aldehydes (acrolein, formaldehyde)	+		
Ammonia	+		
Brick Dust		+	
Cadmium (emphysema)			+
Chlorine	+		
Chloromethyl Methyl Ether	+		
Chromium	+		
Coal Mine Dust (bronchitis, emphysema)	+		
Cobalt		+	
Coke Oven	+		
Cotton Dust	+		
Diesel Exhaust	+		
Endotoxin	+		
Grain Dust (wheat, barley)	+		
Osmium Tetroxide	+		
Oxides of Nitrogen		+	
Paraquat			+
Phosgene	+		
Polychlorinated Biphenyls		+	
Pottery Dust	+		
Sodium Hydroxide	+		
Toluene Diisocyanate	+		
Tungsten Carbide		+	
Vanadium		+	
Vinyl Chloride Monomer		+	
Western Red Cedar	+		
Wood Dust	+		

effect relationships. Despite these considerations, associations between doses and durations of exposure to environmental agents have been made in clinical and epidemiological studies.

Causative agents from occupational exposure comprise two groups (Table V-1). The first includes specific chemicals which produce changes in the airway: ammonia, arsenic, chlorine, osmium tetroxide, phosgene, tungsten carbide (hard metal), vanadium and perhaps sulfur dioxide, toluene diisocyanate, and chlorinated hydrocarbons. The second includes complex dusts which occur in industry: cotton and flax dust,

coke oven emissions, cement dust, foundry dust, ceramic (including brick and refractory ceramic dust), dust from quarries, tomb cutting, and rock crushing operations, metal smelting, both ferrous and nonferrous, and finally a mixed category including potash and phosphate rock, asbestos, and silica exposures combined with one of the above.

A burden of particles, in the absence of a specific toxic agent, may be considered a probable cause of chronic bronchial changes with clinical chronic bronchitis including airways obstruction. Examples include brick making,

grain dust, rock crushing for sand and gravel, and underground mining, particularly of coal (78).

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

Estimates of populations at risk (presumed exposed) and some prevalences of chronic bronchitis and of emphysema are listed in Table V-2. Although the numbers of workers potentially exposed are listed, little data is available on incidence or prevalence. Even in well studied groups such as coal miners, foundrymen, and cotton textile workers, prevalences vary widely within and across studies. In addition, cigarette smoking is often a confounding factor.

Important occupational exposures include gases such as ammonia and chlorine, nitrous fume (8), chloromethyl methyl ether (120), toluene diisocyanate (93)(119), cotton dust (9)(74), Canadian red cedar dust (16)(17), and a variety of dusts or particulate carriers of chemicals such as are found in diesel exhaust (60), cement making (103), tungsten carbide (21), the atmosphere of foundries (24), and various other mining, crushing, quarrying, or smelting operations (25)(35)(82).

EPIDEMIOLOGY

Chronic bronchitis was described by Badham in 1813, by Laennec in 1819, and by Collis in 1923 (cited by Thurlbeck (114)), but its importance and prevalence gained widespread recognition and acceptance only after the studies of Goodman (38), Reid and Fairbairn (95), Oswald et al. (90), and Fletcher et al. (32), beginning in the 1950's. A broad picture of British workers emerged including the relationship of chronic bronchitis to outdoor employment, to environmental pollution, to cigarette smoking, to social class, and to various occupations. Advancing age and male sex appeared to increase the prevalence of both chronic bronchitis and emphysema (54)(59). (Perhaps an appropriate summary is that the lung reflects the cumulative history of its interaction with environmental exposures.) The interplay of some of these factors has been analyzed in two types of patients with chronic bronchitis: those with cough and chronic phlegm production, and those with these two features plus dyspnea. The first appears to have a long, variable period before impairment. However, victims with airways obstruction measured by a decrease

in the FEV₁ or dyspnea so severe as to restrict walking on level ground exhibit a degree of disease likely to progress rapidly to death. Individuals who retire in either Great Britain or the United States with chronic bronchitis and/or disability have a higher death rate. In fact, Smith and Lilienthal showed that only 70% remain alive four years after receiving disability retirement under Social Security (110).

Data concerning the latent period (before impairment) is difficult to find. Glynn correlated pathologic changes with years of bronchial hypersecretion symptoms and found it took more than 10 years for slight changes and greater than 20 years for marked changes in bronchial mucosa (37). Gregory found that the latent period between symptoms and disability, as measured by two or more periods absent from work in 340 foundrymen, diminished progressively as age advanced (42). An overall latency period was meaningless as it was clearly age related in these foundrymen. Bates found that Canadian World War II veterans with chronic bronchitis did not deteriorate until after the onset of dyspnea or reduction in expiratory airflow (7).

Because a clinical criteria definition of emphysema has not been epidemiologically ratified, there are no prospective studies from which one could deduce latency periods or estimate rates of impairment, insufficiency, or disability. This difficulty may be more illusory than real if one accepts the premise that chronic bronchitis and emphysema are highly interrelated; share many etiological factors; have dyspnea as a signal of important dysfunction; and have a similar course regarding both type and rate of progression. Additionally, the progression of both chronic bronchitis with dyspnea and emphysema, although more frequently insidious in development, may occur by damage to one, a few, or many respiratory units. Damage to a given unit may go swiftly to either functional amputation or repair. Because the number of respiratory units (about 64,000 secondary lobules) is high, the lung has a large functional reserve. Loss of individual units could produce insidious progression; loss of many would elicit symptoms and episodic progression. The loss of respiratory reserve implies greater liability for death from pneumonia or respiratory failure, but is also compatible with a long period of serious disability prior to death. As Gilson has pointed out, evidence that cigarette

Table V-2
SUMMARY OF SELECTED OCCUPATIONAL HAZARDS WHICH PRODUCE LUNG DISEASE

Hazard	Occupational Source	Acute Effects	Chronic Effects	Number Exposed	Risk
AMMONIA	Ammonia production, manufacture of fertilizers, chemical production, explosives	Immediate upper and lower respiratory tract irritation: pulmonary edema	Repeated exposure may produce chronic bronchitis	500,000*	
ARSENIC	Manufacture of pesticides, pigments, glass, alloys	Bronchitis	Evidence that it may produce lung cancer, bronchitis, laryngitis	1,500,000*	
CADMIUM OXIDE	Welding, manufacture of electrical equipment, alloys, pigments, smelting	Cough, pneumonia	Emphysema, Cor Pulmonale	2,000*	
CHLORINE	Manufacture of pulp and paper, plastics, chlorinated chemicals	Cough, hemoptysis, dyspnea, tracheo-bronchitis, bronchopneumonia		15,000**	
CHROMIUM (VI)	Production of chromium compounds, paint, pigments, reduction of chromite ore	Bronchitis, nasal irritation	High incidence of lung cancer among workers	175,000*	
COAL MINE DUST	Coal mining		(Pneumoconiosis) Pulmonary Fibrosis, Chronic Bronchitis	200,000	4%-46%
COKE OVEN EMISSIONS	Coke production		High incidence of lung cancer, chronic bronchitis	10,000*	Relative risk of lung cancer about 9 times of other steel workers

Table V-2

SUMMARY OF SELECTED OCCUPATIONAL HAZARDS WHICH PRODUCE LUNG DISEASE (Continued)

Hazard	Occupational Source	Acute Effects	Chronic Effects	Number Exposed	Risk
COTTON DUST	Cotton mills	Tightness in chest, wheezing, dyspnea	(Byssinosis) reduced lung function, chronic bronchitis	800,000*	2%-30%
OSMIUM TETROXIDE	Chemical and metal	Bronchitis, bronchopneumonia		3,000*	
OXIDES OF NITROGEN	Welding, silo filling, explosives manufacturing	Pulmonary congestion	Permanent damage from repeated exposures	1,500,000* Directly or indirectly	
PHOSGENE	Production of plastics, pesticides, chemicals	Pulmonary edema	Chronic bronchitis	10,000*	
TOLUENE DIISOCYANATE	Manufacture of plastics	Acute bronchitis, bronchospasms, pulmonary edema		40,000*	
VANADIUM	Steel manufacturing	Upper and lower respiratory tract irritation	Chronic bronchitis	10,000*	

*Estimate from NIOSH Criteria Document

**Estimate made by NIOSH, 1974

Source: (15)(92)

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smoking cessation improves symptoms and may arrest chronic bronchitis is considerably stronger than evidence that removal from occupational exposure will have an effect (36). Interpretation of this data is difficult because there are insufficient prospective studies in which patients are stratified with or without the dyspnea-airways obstruction component. Experience recommends that removal from dust exposure should alter the reactive component of the symptoms complex, i.e., sputum production. However, unless this substantially improves ventilation to the small airways by removing mucous plugs, or decreases the formation of irreversible, connective tissue scars, improvement would not be expected. The rate of deterioration may, however, diminish.

Cause and effect in multi-causal diseases such as chronic bronchitis and emphysema are difficult to delineate. One serious difficulty is interpreting cross-sectional data on survivorship populations and employed groups. Workers have better function and less disease than the general population from which they are drawn. Furthermore, an occupational cohort is a survivorship of this initial population, and the majority would be expected to have little or no disability (unless the disabled worker remains in the environment for economic reasons.) Even after segregating these into groups on the basis of age, smoking, and dust exposure, they show lesser decreases in function along an advancing age gradient than would be expected from age alone. This reflects selection *out* of the working population of the less functional and less well workers (36)(47)(51). There is more bronchitis in urban than in rural populations drawn from the same ethnic background, and this difference is greater in Great Britain and certain European communities than in the United States. Furthermore, there seems to be an urban factor which remains after adjustments are made for cigarette smoking and air pollution (54)(65). Studies show that among nonsmokers there is more chronic bronchitis among men than women. Day to day variations in levels of air pollution may affect spirometric function measurements more than the five-year aging effect that was reported from a study in Cracow (F. Sawicki, personal communication).

Notwithstanding these complicated relationships, it has been clear since 1953 that workers in certain occupations—particularly coal mining, foundry work, ceramics and cement, cot-

ton and linen textiles, and outdoor labor and construction—have more chronic bronchitis than can be accounted for by the factors enumerated. Therefore, their disease prevalence must be attributed to particles(s) exposure during work (38). Although a correlation between bronchitis and cumulative dust exposure (estimated from chest radiographs graded for pneumoconiosis) has been shown in some studies, this relationship is also complex. A study by Rogan et al. of a group of 3,581 coalface workers showed that the greatest reductions in FEV₁ were attributable to increasing cumulative exposure to airborne dust (100). This was evident in subjects who had no chronic phlegm and cough symptoms. This study suggests that chronic hypersecretion of mucus is protective and that coalface dust and cigarette smoking were simply additive. Cigarette smoking and occupational dust exposure interaction studies lack data concordance. Higgins and Cochrane found almost no relation between symptoms of bronchitis and the radiological category of pneumoconiosis, but they did find a downward trend in the indirect maximal breathing capacity with increased time spent on the coal-getting shift underground (47). There was a large effect of cigarette smoking, but after this was corrected, miners still had more chronic bronchitis than nonminers. In two integrated steelworks in industrial South Wales, Lowe et al. (69) and Warner et al. (118) found an overriding contribution of cigarette smoking in producing chronic bronchitis. Although they used a number of analytical techniques to stratify population exposure to SO₂ and respirable dust, they could find no convincing effect that SO₂ exposure produced chronic cough and phlegm. Returning again to miners, Higgins et al. showed that cigarette smokers had a higher prevalence of cough and sputum than nonsmokers in West Virginia (50). However, the highest prevalence of breathlessness, chest illness, and chronic bronchitis was found in a group of pottery workers including nonsmokers presumably exposed to silica and other glazing particles. One of the first studies of foundrymen by Higgins et al. showed that they had only slightly higher prevalences of bronchitic symptoms than men who had worked in dust free occupations (48). Although miners had a significantly higher prevalence of respiratory symptoms and lower maximum breathing capacity, the effect of even light cigarette smoking was more important than either of the in-

dustrial exposures. There are important co-factor effects. Cigarette smoking was associated with the following four factors in coal miners: irregular opacities in chest radiographs, bronchitis, age, and years underground (3). In Britain, Davies looked at 1,997 foundrymen compared with 1,777 control workers in engineering factories (24). The foundrymen showed increased respiratory symptomatology (defined as production of sputum for more than three months a year, or one or more attacks of chest illness in the past two years); 10.5% of the foundry floormen and 10.9% of the fettlers exhibited such signs as opposed to 7.2% of the controls. The effect of smoking added to the effect of the foundry environment. A regression line for FEV₁ and VC on age for foundrymen without the sputum-chest illness syndrome fell significantly more steeply between the ages of 35 and 64 than it did for controls. A small effect of dust exposure on chronic bronchitis during gold mining was found in South African Bantu workers, of which 45% were nonsmokers. Of the whites, 19.5% had chest illness, plus cough and phlegm, compared to only 0.8% in Bantu. Rates for cough and phlegm alone were 39.3% vs. 3.5%. However, the authors suggested that culture, language, and race may have biased these results (108).

Emphysema

Several reports since 1950 have ascribed emphysema to cadmium fumes, particularly in workers exposed to cadmium oxide over prolonged periods of time (11)(33)(66)(109). At 3-15 mg/m³ exposure to cadmium dust, Friberg found 23 of 43 workers with RV/TLV ratios above one standard deviation from the mean; 15% were greater than 35% (33). Of two deaths, one had emphysema, the other pulmonary edema and cor pulmonale. Seven autopsies (2, (66); 1, (33); and 4, (109)) showed well developed emphysema in cadmium workers. However, the definitive cause is ambiguous because cigarette smoking histories were not given and each worker had exposures other than cadmium (coal mining, charcoal burning, foundries, ceramic kiln and copper casting). Recent studies of worker exposure to cadmium oxide in the alkaline battery industry showed less evidence of respiratory impairment (1)(104), but proteinuria, impaired renal function, and osteomalacia were seen. Adams et al. found the FEV₁'s were at the lower end of predicted in 27 workers at a cadmium bat-

tery plant in Birmingham, England (1). Kazantzis et al. studied 12 workers from a cadmium pigment factory and found only 3 with reduced FEV_{1,0} and increased RV/TLC ratios compared to proteinuria and evidence of renal tubular dysfunction in 8 (62). Thus there is some evidence for respiratory impairment from chronic cadmium exposure although the evidence for emphysema is equivocal. The latest study of 17 men exposed at levels of 0.2 mg/m³ for 6 years or more showed 5 (29%) with fibrotic changes on x-ray and reduced FVC, but no data on RV or TLC (111). This is because smoking histories were not recorded, and published studies included no long-term prospective study with adequate pathologic material. Cadmium is in cigarette smoke; in subjects without occupational exposure, it accumulates in the lung from this source at tissue levels related to cigarette smoking (52) (68)(84). Thus it is impossible to determine whether cadmium produces emphysema in workers exposed at current industrial levels. Cadmium effects on lung were shown in rats exposed to 0.1% cadmium chloride aerosols for 15 days. Mean alveolar intercept increased 40%, and alveoli developed a pattern resembling centrilobular emphysema (112).

Does emphysema in coal workers represent the coexistence of emphysema due to cigarette smoking in miners with or without pneumoconiosis, or is it due to exposure to coal? Studies have established that emphysema, most frequently centrilobular in type, occurs in coal miners autopsied in Great Britain and the eastern United States. By matching 2,000 miners to non-coal mining controls, Ryder et al. showed that there was more emphysema and that emphysema was more advanced by point-counting in individuals who had higher pneumoconiosis scores (101). Smoking effects were not examined. Naeve also looked at postmortem comparisons in U.S. coal workers and found that controls had 4.8% of their lung involved by emphysema; nonsmoking coal workers 24.3%; and smokers 30.2%—a statistically significant difference, $p > 0.05$ (83). Attempts to relate emphysema to radiographic hyperinflation have shown that in 1,455 working miners, the total lung capacity estimated from the chest radiograph was correlated with higher categories of coal workers' pneumoconiosis. Increasing residual volume was spirometrically found both in the presence and absence of obstruction, although the obstruction

effect increased the residual volume further (80).

The type of coal and mine locale have differing effects upon the prevalence of coal workers' pneumoconiosis. The prevalence of simple pneumoconiosis is 45% and progressive massive fibrosis 14% in eastern Pennsylvania anthracite miners, whereas Colorado bituminous miners exhibit 4.6% and 0% (79). Because studies show that dust levels and underground exposure durations affect chronic bronchitis prevalences, the quality of coal mined and/or environmental drilling conditions may have as large an effect on emphysema and chronic bronchitis as they do upon coal workers' pneumoconiosis.

PATHOLOGY

In this section the pathological features of chronic bronchitis are described; pathogenesis and pathophysiology are discussed and correlated with clinical findings. Emphysema will be described in the same sequence as will an interpretation of the combined chronic bronchitis-emphysema disorder.

Chronic Bronchitis

The division of chronic cough and sputum production—the hypersecretion syndrome described by Fletcher (32)—into finer gradations based on mucoid sputum, purulence of sputum, obstruction measured by pulmonary function tests, and the presence of dyspnea has been advocated and has some usefulness. In chronic bronchitis, hypersecretion of mucus or phlegm correlates with altered epithelium in the airways which may extend from the trachea to the terminal bronchioles. The alterations consist of goblet cell squamous metaplasia and hyperplasia. The other cardinal finding is mucous gland hyperplasia, a concept introduced by Reid (the Reid Index (97)) who demonstrated a correlation between the volume of mucus and the proportion of distance between cartilage and airway epithelium occupied by mucous glands. Airways obstruction and dyspnea have little if any correlation with mucous gland hyperplasia. But dyspnea, usually due to airways obstruction, is correlated with goblet cell metaplasia, and the spread of goblet cells past the 12th bifurcation (the normal termination of goblet cells and cartilage) into distal terminal bronchioles. There was goblet cell metaplasia in a majority of the small bronchioles of patients who died of respiratory insufficiency due to chronic bron-

chitis (61)(115). Such replacement of Clara cells by goblet cells in small airways also characterizes cigarette smokers' lungs removed surgically (26). Other early features, including leukocytic infiltration of the epithelium; its absence or at least interruption; fibrosis; hyperplasia of smooth muscle; squamous cell metaplasia; and airways obstruction, with or without mucus, are seen frequently in patients who have pulmonary function tests indicating small airways obstruction (22). A potentially reversible component of this spectrum is bronchial mucoid impaction (106). A reduction of functioning bronchioles prior to measureable airways obstruction has been described by Bignon et al. (10) and Mitchell (77).

The pathogenesis of chronic bronchitis is not definitively established. Manifestations of increased sputum production and small airways blockade by mucus and subsequently by scarring, may be induced by a variety of environmental agents (classified in Table V-1, page 504). Pathogenesis can be divided into the insidious onset type—which in the case of cigarette smoking takes about 20 years of a pack a day or greater exposure to produce important airways obstruction or dyspnea—and an acute variety which follows severe and abrupt respiratory illnesses. These have the general character of a viral infection with fever and dyspnea but without leukocytosis. The chronic production of large amounts of mucoid, often greenish, sputum begins with these illnesses. Although chronic bronchitis has been studied in groups of workers, histological findings are rare. Edwards et al. studied British textile works and discovered the pathology was indistinguishable from that of nonindustrial chronic bronchitis as described above (27).

Relatively few studies have been directed at the pathogenesis or at the antecedents and prognosis of chronic bronchitis. Gregory studied the life history of men with the disease in a British foundry (42). With the insidious variety, he found that the earlier the age of onset, the longer the latent period until impairment. The abrupt onset variety began at any period of life. A somewhat different perspective was provided by Brinkman and Block who studied industrial workers in Detroit (13). Although the number of workers with cough and sputum production increased during an eight year follow-up period, individuals both entered and left the bronchitic population. There was no accelerated net reduction in

pulmonary function above that expected. Pathologically, lung studies of patients who died in airways obstructive respiratory failure have shown the single most responsible lesion was goblet cell metaplasia in small bronchioles (61) (115). Thus, it may be postulated that the effect of environmental chemicals (as particles) upon the larger airways is to induce mucus production and retard ciliary clearance. For some period of time the manifestations (cough and sputum) remain static as long as the smaller airways are not involved. However, when there is metaplasia of small airways secretory cells into goblet cells, mucus fills these ordinarily nonmucus airway lumens and obstructs them. Similarly, one can have severe damage at this airway level from gases such as ammonia, chlorine, nitrite (8), halogenated hydrocarbons, bromobenzene, PCBs (98), and osmium and develop acute bronchiolitis progressing to fibrosis and obliteration. Careful pathologic studies such as those of McLean (70)(71), and Leopold and Gough (67) favor this pathogenesis.

Pathophysiology Chronic Bronchitis

The crucial question is: what converts a relatively benign symptom complex of cough with sputum production into a serious and potentially fatal illness resulting in carbon dioxide retention, hypoxia, and finally asphyxia? Although it is conceivable that obstruction of airways which already have mucous glands and goblet cells is responsible, these are also the airways cleared by coughing. Unless there is loss of consciousness or severe neuromuscular disease (temporary or permanent), this mechanism seems unlikely. The probable mechanism for progressive chronic bronchitis, with irreversible airways obstruction and dyspnea, is progressive impairment of small airways (terminal bronchioles with luminal diameters of less than 1 mm). These airways have no intrinsic, lumen maintaining, structural features; they are well beyond the distal extensions of cartilage and lack even substantial smooth muscle. They are normally stretched out to a nearly circular cross section on deep inspiration by radial traction from surrounding alveolar ducts and alveoli. On expiration, they infold deeply and appear fluted in cross section. This places the airways' walls in near apposition. So long as the airways' surfaces are coated by nonviscous fluids of low surface tension, they pull apart with minimal

expenditure of pressure, even if they touch during expiration. However, if the fluid is sticky (like bronchial mucus), high pressures must be achieved to separate these mucus-coated, fluted infoldings, and airways obstruction results. Although no model exists, nor have extensive human studies chronicled the step, it is likely that this process, involving airway after airway, subtracts these and the secondary lobules they supply from the lung's gas exchanging capacity system. This probably occurs first because these become late opening secondary lobules and subsequently do not open at all. It is plausible such obstructions lead to another series of changes involving leukocyte recruitment, which provides the potential for enzymatic damage to the epithelium (57). The final stage is probably loss of the epithelial surface; stimulation of the underlying fibroblasts in the lamina propria; and either polypoid lesions growing into the lumen or, if there are more extensive scars, crossing lumens and restricting the luminal cross-sections. If damage is severe and extensive, respiratory failure follows quickly; otherwise it is slow and insidious.

The pathogenesis of acute bronchitis and bronchiolitis caused by viral infections may be a variation on this pattern, with damage to the epithelium. Connective tissue proliferates faster than epithelial repair so that an ulcerated area is repaired with a fibrous scar encroaching or obliterating the lumen rather than by replacement of epithelium. Clearly the epithelial-mesenchymal interface relationship is important; structurally the basal lamina of the airway is crucial. The model for a lesion of this interface is produced by severe airways damage such as the injection of dilute nitric acid into the airways of rabbits. Damage centers upon small airways distal to those protected by mucus and consists of complete denudation of the epithelium (with rapid scarring polypoid lesions) or obliteration of multiple long airways lined by epithelium. The denudation or obliteration encompass only a small fraction of the original lumen. Preliminary experiments suggest that neuraminidase, the active destructive principal of the influenza virus, produces the same type of lesion within a few hours after injection into rabbit airways (Kilburn, unpublished). This is also similar to the lesion produced by brief but higher level exposure to oxygen (87), nitrite (8), and bromobenzene (98). A crucial pathogenic factor seems to be epithelium destruction and connective tis-

sue proliferation from the lamina propria into the luminal space causing obliteration. The presence of mucus within the lumen may be important in the insidious development of small airways disease in chronic bronchitis, but probably has a lesser role in the acute or abrupt onset type.

Pathology of Emphysema

Knowledge of the pathology of emphysema advanced quickly with inflation-fixation and studies of whole lung sections introduced by Gough (39). Observations made before that time, which depended upon the failure of the lung to collapse when the chest wall was removed or upon bullae or blebs under the pleural surface, are practically meaningless. This is not to say that all earlier studies, including the classic description of Samuel Johnson's lung by Matthew Baillie, are useless, but it is important to realize that they used the same basic approach of fixing the lung in inflation.

The secondary lobule (or acinus) of the human lung is a cube or tetrahedron of about 10 mm on a side, bordered by at least an incomplete interlobular septum consisting of collagenous connective tissue. It is supplied with air by a single bronchiole and accompanying arteriole and is the focus and arena for the macroscopic description of emphysema. Enlargement of air spaces within the whole secondary lobule is called pan-lobular (PLE) or panacinar emphysema; enlargement localized in the lobule's center, is centrilobular emphysema (CLE) (40). These are the major types of diffuse emphysema. In CLE there is an absolute reduction of central alveolar walls and a high frequency of pigmentation in central areas of lobules (94). With worsening of the process, the lobules become grossly distended and distort the surrounding, less involved areas producing irregular bullae (46). An overlaid grid or eyepiece graticle is used to subdivide the lung and judgments are made for each subdivision of whole lung slices. These methods are used to describe the extent of emphysema and assess its severity quantitatively (102). Using the conventional classes of 0 = none, 1 = mild, 2 = moderate, 3 = severe for each grid zone, it has been shown that one whole lung section is a satisfactory sample and that more are superfluous (114). A particularly intense form of central pigmentation surrounded by a halo of departitioning characterizes emphysema in coal workers (41)

(122). Scarring of this central focus is usually minimal, but when silica is present it may be extensive, enclosing the black pigment in a stellate scar (45). This perifocal distribution of emphysema around black centrilobular scars is seen particularly in Pennsylvania anthracite miners (83)(122).

Histologic sections of lungs fixed in inflation show numerous islands of connective tissue crossing empty spaces which represent incomplete walls of remaining alveoli within the lobules or, in some cases, the lobular septa or the vessels (46). Observing these changes—which occur in the absence of leukocyte or lymphocyte infiltration, but which are possibly accompanied by some degree of fibrosis—makes it possible to extend the diagnostic technique of looking for isolated islands of tissue in uninflated and poorly inflated lungs (94). However, quantitation is clearly impossible without whole lung sections.

Concepts of the pathogenesis of emphysema have been revolutionized in the past decade beginning with the discovery that papain, a vegetable protease, destroys lung in a pattern resembling that of the naturally occurring disease (43). Biochemical disturbances showing a rapid proliferation of fibrous tissue after papain injury (64) were followed by the demonstration that elastase (rather than collagenase) of animal origin produces both morphologic and functional disturbances resembling emphysema of the naturally occurring type (58). Sources of such elastase have been thought to be polymorphonuclear leukocytes and alveolar macrophages because proteases, which are active at a neutral pH (56), are required. Curiously, evidence of increased cellular recruitment in areas of moderate or early emphysema is infrequently found in the human lung. It is possible, however, that cells have cleared out by the time the damage can be detected with the light microscope. Also, native (resident cell) lung proteases which have been activated by macrophage or polymorphonuclear responses may be the important ones. The balanced relationship of these proteases to cellular and to circulating anti-proteases is important; the predominant ones—alpha₁-antitrypsin and alpha₁-macroglobulin—have received considerable study (29). Both are broadly effective anti-proteases against enzymes from leukocytes and the lung. The possibility that emphysematous lungs may have had abnormal development or

reflect a defect in the stage of alveolarization during organogenesis has been raised by observations that offspring of copper deficient rats have incompletely partitioned lungs with reduced amounts of elastin (88).

Correlation with Clinical Findings

Evidence has been accumulating since 1970 about the types of small airways lesions which correlate with airways obstruction measured by frequency dependent compliance, closing volume and closing capacity, midflow in the flow volume curve, and maximal mid-expiratory flow rate (22)(53). Lesions commonly associated with small airways obstruction involve mucous obstruction, epithelial changes with goblet cell metaplasia, and ulceration in the 1 mm and smaller terminal bronchioles. It appears that 50% or more of these airways must be functionally impaired by goblet cell metaplasia before airflow impairment is detectable. Whether dyspnea (particularly breathlessness with exertion) occurs earlier or simultaneously with these objective measures has not been investigated in a population. The answer to this question has important implications for choosing screening and surveillance methods for occupationally exposed populations.

Correlation of emphysema pathophysiology with clinical findings has not been approached prospectively either. Studies which have depended upon abnormalities of pulmonary function (such as reductions in relaxation pressure and leftward shift of the pressure-volume diagram, i.e., increased compliance) have not proven to be effective indices of dyspnea grades in studied populations. Also the number of subjects studied has been small. If an emphysema population is selected from hospitalized patients on the basis of x-ray changes, dyspnea on exertion is almost universal. This criteria has not been prospectively applied to a population of employed or retired people. Studies to date have been on hospitalized populations. By the time absolute anatomic criteria are met, based on macrosections of lungs fixed in inflation, one is dependent upon chart review for ascertaining the presence and severity of dyspnea. This yields unsatisfactory data. Whether or not dyspnea precedes measurable functional abnormality or radiological changes in people with barely detectable emphysema cannot be answered, but it is unlikely for the category in general.

CLINICAL DESCRIPTION

In this section, the symptoms, signs, and natural history of chronic bronchitis are discussed, then those of emphysema, and finally, modifications in the patterns which would be produced by the presence of both disorders together.

Symptoms

The cardinal manifestation of chronic bronchitis is sputum production, persisting or recurrent over a period of time. Cough is the other key complaint. The sputum or phlegm may be mucoid or purulent. Purulence manifested by yellow or green color reflects an abundance of polymorphonuclear leukocytes. Asthmatics with marked sputum eosinophilia may have yellowish sputum without infection. Dyspnea on exertion divides progressive chronic bronchitis (the airways obstructive disorder) from the indolent (hypersecretory) type. Such breathlessness in the presence of chronic phlegm production specifies a different prognosis with more rapid reduction of expiratory airflow over a passage of time. Thus, although the presence of phlegm and cough indicates a population of individuals responding to airways insult with hypersecretion, it does not by itself indicate the seriousness of the disorder or its prognosis (32). In contrast, the presence of dyspnea is a serious signal. Dyspnea implies progression toward insufficiency at a far greater rate than the deterioration of a normal population, or those who are cigarette smokers alone, or those with cough and phlegm without dyspnea. Serious hemoptysis is unusual, but blood streaking is common in chronic bronchitis. It occurs without relation to dyspnea or airways obstruction. A subpopulation of dyspneic chronic bronchitics wheeze and have intermittent, partly reversible airways obstruction. Their airflow is often improved more than 15% by bronchodilators and by adrenal corticosteroids.

Signs

The cough of chronic bronchitis should be characterized by the listener as either wet (productive) or dry (nonproductive); the former correlates with persistent sputum and impairment (34). The chest has a normal configuration; the diaphragms are in the usual position at the 10th rib or 10th intercostal space posteriorly. Expiratory time may be lengthened; in its early phase

there may be coarse rales or rhonchi. When symptoms are minimal, breath sounds are generally normal, but they are decreased in the advanced stages. Fine rales, early in inspiration, are frequent and may be accentuated by deep breathing and by a deep breath after an end expiratory cough, particularly in patients with dyspnea. Usually there is a gradient of signs: prolongation of expiration, decrease in breath sounds, and the presence of fine rales increasing with the severity of the disorder. Because clubbing of the digits is unusual, its presence should alert one to bronchiectasis or a mass lesion. Chest pain indicating pleural involvement is rare except with definite pneumonia. Cyanosis is rare until the disease is greatly advanced and then reflects hypoxemia and peripheral vasodilation due to hypercapnia.

The Natural History of Bronchitis

The natural history of bronchitis is of two types: one with an abrupt onset and the other with an insidious onset. With abrupt onset, the individual has a respiratory illness—usually viral in character—with fever, malaise, shortness of breath, and cough and produces copious, intense green sputum. Occasionally this stage is fatal, apparently due to massive obstruction of small airways. The majority of patients recover and thereafter are sputum producers. This type of disease has no relation to cigarette smoking or to other specific exposure and is seen frequently in women.

Insidious onset develops with or without chronic cough upon arising in the morning. There is often some sputum production which may slowly advance to more productive cough with a greater amount of sputum. However, dyspnea may develop insidiously without symptoms of hypersecretion. Although there may be recovery, even after several years of hypersecretory symptoms, once dyspnea is established, recovery is rare. After an interval (which seems to shorten with advancing age of onset, e.g., it is only 5 years at age 55 versus 25 years at age 25) dyspnea develops. At first it develops on severe exertion; then it gradually worsens (42). At this time, signs of airways obstruction can be found and the disease enters an inexorable, progressive course, culminating with respiratory insufficiency and often death from respiratory failure.

Symptoms, Signs, and Natural History of Emphysema

Emphysema's principal symptom is dyspnea, noted first during severe exertion, but then elicited by lesser degrees of activity. In the absence of bronchitis, cough is nonproductive and usually a minor symptom. Hemoptysis and chest pain are unusual.

The signs of emphysema increase in severity just as they do in bronchitis. In well developed disease, diaphragms are low and relatively fixed in position; i.e., they move poorly with inspiration and ascend very little with expiration. Expiration is prolonged and may exceed 15 seconds. Breath sounds are decreased and may even be absent, except for bronchial sounds heard directly over the major airways. Fine rales may be present in the lung bases, but generalized rales are unusual. Systemic manifestations include wasting of the body and pink-white skin, without cyanosis until very late in advanced disease. Finger clubbing is unusual and indicates pleural or parenchymal mass lesions or another disease such as bronchiectasis.

The natural history of emphysema after clinical recognition (which is usually late) is variable. There are patients whose conditions remain clinically static for many years with dyspnea on mild exertion and extremely reduced pulmonary function. However, the usual course is one of inexorable progression, complicated by increased impairment due to intercurrent respiratory illnesses which exacerbate the already severe dyspnea. The frequency with which chronic bronchitis and emphysema occur in the same individual has led to the proliferation of nonspecific terms such as chronic obstructive airways disease, chronic obstructive pulmonary disease, chronic obstructive lung disease, etc. Non-specific terms should be avoided. Patients with combined disease should be designated by the relative contributions made by emphysema and by chronic bronchitis.

Laboratory Investigation

The major physiological impairment of subjects with chronic bronchitis is irreversibly decreased expiratory airflow as measured with a spirometer from a forced expiration from full inflation, i.e., the forced vital capacity (FVC). Early impairment is recognized by reductions in maximum mid-expiratory flow rate (flow 25-75)

or flow at 50% of volume. Later, the forced expiratory volume in one second ($FEV_{1.0}$) is reduced and as airflow obstruction becomes moderately severe, forced vital capacity (FVC) is decreased. Airways resistance requires more complex and elaborate apparatus for measurement such as a body plethysmograph; it is elevated earlier than flow rate changes. In general, the more sensitive measurements have the greatest variation, so $FEV_{1.0}$ remains preferable for population studies. The response to bronchodilators is no greater than in normal subjects: there is less than a 10% improvement in flow rates after isoproterenol or equivalent aerosols. Reductions in expiratory airflow over a work shift indicates exposure effects, as shown for toluene diisocyanate (TDI)(93) and cotton dust (75).

Total lung capacity (TLC) is generally normal or slightly decreased; lung volumes including functional residual capacity (FRC), retain normal proportions. Diffusing capacity for carbon monoxide (D_{CO}) is at or slightly below predicted levels in the hypersecretory phase, reflecting preservation of gas transferring alveoli. It decreases relatively late in the course of dyspneic airways obstructive disorders. In the author's experience, the single breath D_{CO} is preserved longer than the steady state D_{CO} measured at exercise, perhaps reflecting alveolar preservation despite small airways obstruction. Resting hypoventilation, due to increased breathing work, is absent in cough and phlegm disorders, but develops in dyspneic cases. It is manifested by an increase in the carbon dioxide tension of arterial blood. Carbon dioxide retention may occur when the oxygen tension is only mildly depressed.

In emphysema, the principal pulmonary functional abnormality is an increase in total lung capacity which is associated with low, flat diaphragms on typical chest radiographs (as if the chest were held in inspiration). Early in the course, when increases in TLC and FRC are just detectable, the vital capacity may be normal, but as the disease progresses, vital capacity is reduced as TLC and FRC increase further. At approximately this time, flow rates on expiration are decreased and follow a pattern which is then similar to that described for chronic bronchitis. This probably occurs when more than 50% of small airways, and terminal bronchioles, have lost radial traction around part of their cir-

cumference because of alveolar loss. The unsupported areas of these airways obstruct airflow because they open late in inspiration and close early in expiration.

Conjecturally, the diffusing capacity might be the first of the gas transfer tests to show abnormality and ought to do so at approximately the same time as the total lung capacity increases (117). The problem is that the Gaussian distribution for normal has such wide limits, it is difficult to detect loss of pulmonary function unless previous data comparisons can be made on the same individual. Diffusing capacity (reduction) and total lung capacity (increase) changes ought to occur before symptoms develop or even before chest radiographs are diagnostic. As emphysema progresses, the diffusing capacity, both single breath and steady state methods, is progressively reduced, and hypoxemia stimulates hyperventilation so there is a corresponding reduction in carbon dioxide tension. Thus, the early disease is characterized by a low carbon dioxide partial pressure as the oxygen partial pressure progressively decreases below 70 torr. When emphysema is complicated but associated with acute or chronic bronchitis or reaches the end-state, arterial blood tension may rise to or exceed normal. However, in the patient without sputum production, a high CO_2 (i.e., above 55 mmHg) is not seen unless he has been given oxygen, a central nervous system depressant, or has suffered primary damage to the central nervous system. Hypercapnea is most frequent after subjects have received sedatives or narcotics.

Radiographic changes are absent in chronic bronchitis. It has been suggested that broncho-pulmonary markings are increased, particularly in the lower lobes; that there is gathering of broncho-pulmonary markings toward the mediastinum, particularly in the lower lobes; and that tracheal wall shadows are thickened. However, attempts to validate these observations by intermixing diagnosed chronic bronchitic patients with subjects of the same sex and age without chronic bronchitis have revealed them to be non-specific. Plain chest radiographs do not aid in the diagnosis of chronic bronchitis except by excluding localized disease such as pneumonia, abscesses, tuberculosis, or neoplasm. Bronchography may be helpful. Two changes are frequently, although not exclusively, seen with chronic bronchitis: (a) The absence of the peri-

pheral filling of small bronchi and bronchioles (the so-called peripheral pruning pattern first named by Simon and Galbraith)(107);* (b) The filling of lumens and even acini of the bronchial mucous glands of major bronchi. Such filling is virtually diagnostic of chronic bronchitis and reflects hypersecretion by the mucous glands. However, bronchography is seldom indicated solely to confirm the diagnosis of bronchitis and can precipitate respiratory failure in those with severe impairment.

The characteristic radiographic changes of emphysema are of two general types: an increase in the volume of the thorax occupied by lung and a decrease of the overall pulmonary vascular pattern. These organize into four major criteria (113). The two criteria on posteroanterior radiographs are: 1) flat and depressed diaphragms, i.e., flat for $\frac{2}{3}$ of their diameter below the 10th intercostal space, and 2) radiolucent or avascular areas including the presence of bullae or blebs. The two criteria on lateral radiographs are: 3) low flat diaphragms—flat is taken to be more than 50% of the extent of each diaphragm, and 4) a retrosternal space between the sternum and the aorta of 2.5 cm or greater. Tomography and angiography will confirm an altered vascular pattern and presence of large bullae or blebs. The chest contour is not basically altered in emphysema. Although the barrel chest has been repeatedly described, it is the contrast of general body wasting, together with a scaphoid abdomen, which can make the chest appear prominent; it is *not* increased absolutely (63).

Other investigations include studies of serum anti-proteases, particularly α_1 -anti-trypsin in emphysema. Only approximately 1:2,000 of the U.S. population are homozygous for α_1 -antitrypsin deficiency (zz) so this defect does not correlate with most of the emphysema seen in the population. Whether heterozygosity with intermediate levels of antiproteases increases the risk for emphysema is uncertain, but it seems unlikely.

Examination of the sputum is useful in chronic bronchitis (19). Normal secretions (those obtained by bronchopulmonary lavage from normal subjects) show 95% alveolar macrophages and about 5% epithelial cells, most of

*This absence of filling was further studied by Reid (96), and she added the presence of peripheral pools which is the collection of bronchographic media in dilated small bronchioles.

which are ciliated. In chronic bronchitis, the alveolar macrophage proportion falls as the total number of cells and proportion of leukocytes goes up by several orders of magnitude and more during exacerbations (18). In addition to the increase in numbers, the cell type changes from 95% alveolar macrophages in normals and in patients with alveolar disease (including those with emphysema) to a 35% or greater ratio of polymorphonuclear leukocytes. These cells often show granulation, loss of cell walls, and isolated nuclei without cytoplasm. The second consistent change is alteration of the exfoliated epithelium—particularly the presence of squamous cell sheets due to exfoliated areas of squamous metaplasia. Squamous cells and goblet cells thus replace the normal ciliated cells. There also may be clumps of goblet cells and usually an increased number of ciliated cells, so that the sputum's epithelial population is usually above its normal 4% or 5% of the total cells. Eosinophils may constitute 1%-3% of cells in chronic bronchitis, but over 5% usually indicates asthma.

Treatment

The treatment of chronic bronchitis has two basic tenets: 1) reduce irritants which stimulate mucus production by hyperplastic goblet cells and mucous glands, and 2) improve sputum delivery and clear airways. For most patients, particularly those with bronchitis of insidious onset, the most important way for them to reduce irritation is to stop smoking cigarettes. The consequence of this step cannot be over-emphasized. Each milliliter of mainline smoke contains two billion particles. Reductions of occupational exposure or general air pollution, in the absence of smoking cessation, probably have little benefit except for those specific exposures highly correlated with chronic bronchitis: cotton dust exposure, coal mine dust exposure, etc. There is obvious logic to reducing exposure to the other specific agents, including ammonia, chlorine, aldehydes, phosgene, and irritant dust. Improvement of delivery or removal of sputum depends on increased liquification and better cough volume and velocity. The first is accomplished best through increased oral fluid intake so that dilute, pale urine is produced. This insures fluid for airways moistening. This fluid is delivered beneath the mucus secretions on the surface of cells and is far more effective in aiding clearance than any aerosol delivered onto the impervious

mucous layer. Second, bronchodilator drugs such as epinephrine, isoproterenol, and xanthines (aminophylline) improve lung inflation and decrease work so that coughing is more effective. Ciliary action may also be stimulated by certain B₂ adrenergic drugs such as terbutaline sulfate. Additionally, acute episodes of superimposed bacterial bronchitis should be promptly treated with an antibiotic such as tetracycline, ampicillin, or a trimethoprim-sulfamethazole combination.

The aim in treating patients with emphysema, but without sputum, is to relieve dyspnea. This is partly an educational program: to teach the patient to live within his limitations. This should be done with care so that the limitations do not become an excuse for general deconditioning and a vicious downhill cycle. Concepts of pacing activities within capacity and of striving toward levels of slight to moderate dyspnea, before stopping/resting are useful to avoid (patient) anxiety which wastes ventilation. Conscious control of respiratory effort is important for economical breathing. The approach is similar to that for patients with angina pectoris, but dyspnea is the gauge instead of pain. Strategies such as conscious overbreathing before ascending a staircase may help match ventilatory exchange with increased muscular effort. If dyspnea is elicited by minor stresses (including emotional ones), it is important the patient have a personal means to relieve it. This may be a simple hand-held nebulizer or may require a mechanical respirator to reduce the work of breathing. In most cases, use of intermittent positive pressure devices provides little or no additional benefit over nebulizers for delivery of medication. Chest physiotherapy has two virtues: (a) making breathing conscious so the patient realizes it is under his control, and (b) shaking loose secretions and improving cough efficiency. Postural drainage is an important part of the latter in some patients although it works best in patients with pooled purulent secretions which are not sticky. Breathing exercises may condition the subject to maintain low respiratory rates during stress and thus avoid aggravation of ventilation maldistribution. Beyond this they are of no benefit.

Prognosis

One of the earliest studies of prognosis in bronchitis was that of Reid and Fairbairn who

studied the records of 565 postmen who had retired prematurely because of chronic bronchitis and 45 postmen who died from that cause during 1950-1954 (95). The 517 who were granted pensions were followed for periods up to 7 years and the causes of death ascertained in the 124 who died. In this study, patients with chronic bronchitis had longer absences from work, and after age 45, they had many attacks of pneumonia, pleurisy, and asthma along with circulatory disorders—including coronary artery disease and peptic ulcers. Unfortunately this study had no data on smoking habits. The link of chronic bronchitis with cigarette smoking was confirmed in a 1953 study. The death rate in smoking, chronic bronchitics was 4.2 times that expected in males and was chiefly due to respiratory causes (73). In 1,000 chronic bronchitis patients surveyed in 1953, more than half had cut down on their cigarette smoking because they found it aggravated their bronchitis.

Other important factors were the combustion of hydrocarbons such as coal and oil as in motor car exhaust, sulfuric acid, acetone, benzene, caustic soda, and paint spraying and irritant particles including asbestos, corkwood, lead, lime, marble, printer ink, talc, and chromium. Fletcher found occupation and social class were important in mortality related dust exposure; laborers led the list followed by road transport workers and steel foundrymen, coal and other surface workers, coal miners, foundrymen, metal molders and casters (30). The wives had similar standardized mortality ratios and although this was attributed to social class and/or economic factors, including quality of and site of housing, it might also include effects of dust brought home on work clothes—as has been shown to be true for asbestos. Higgins et al. studied respiratory disease and found that mortality of smokers from all causes was approximately twice that of nonsmokers (49). In addition, they showed the average annual decline in the 0.75 second forced expiratory volume was greater in older than younger men (0.058L vs. 0.032L) and appreciably greater in smokers (0.037L) than in nonsmokers who showed only 0.021L in the 25-34 age group and 0.044L vs 0.032L in the 55-64 age group. In these British studies the population considered to have chronic bronchitis had both hypersecretion and breathlessness. Hyatt et al. showed that 10 or more years underground reduced the MMEF 25%-75% for coal miners

at 0-10, 10-30 and >30 pack-years of cigarette smoking (56).

In the United States, Brinkman and Block prospectively studied 1,317 men employed in industries in Detroit (13). They were examined in 1958 and again in 1964 by questionnaire, spirogram, and chest roentgenogram. The diagnosis of chronic bronchitis was based on a daily cough for at least the preceding 6 months, productive of at least a teaspoonful of sputum a day. The first important finding was that a population with silica dust exposure, largely foundrymen, had a bronchitis rate in 1958 of 36% and in 1964 of 45%. These were men with radiographic evidence of silicosis. Foundrymen without such evidence had a rate of bronchitis in 1958 of 16% and in 1964 of 36%. In contrast, for workers with no silica dust exposure, the 1958 rate was 21% and the 1964 rate 27% as compared with hospital workers who had a rate of 32% in 1958 and 16% in 1964. The bronchitis rate went up from 15% in the age group 40-44 to 24% in the age group 60-64, and it went up with increase in smoking from 11% to 25% for nonsmokers to heavy smokers in the 40-44 age group and 14-39% in the 60-64 age group. There was slightly more dyspnea at each age group and at each grade of silicosis in the bronchitics than the normals, but this was statistically insignificant. However, there was a clear relationship between increased grade of dyspnea and reduction in FEV_1 and MMEF.

Worth et al. in a study of coal miners, foundry workers, chemical workers, and bakers found a strong relationship between tobacco consumption and cough, and a relation between dust and cough and phlegm (121). When dyspnea was considered, age had a major influence, as it did on vital capacity, $FEV_{1.0}$, and arterial oxygenation. Enterline studied occupation together with bronchitis and emphysema in two West Virginia coal mining towns and compared standard mortality ratios (28). He found that both men and women in heavily polluted areas (where higher ranked coal was mined) had more cough, phlegm, and breathlessness than nonmining industrial workers and their wives. There was also a difference between the miners in the two communities suggesting an effect of air pollution. Cigarette smoking was comparable with coal miners smoking slightly less than other manual workers. Excess deaths occurred in men with reduced ventilatory capacity when standardized mortality ratios for all deaths for 4,004 Pennsylvania coal miners

awarded compensation for coal workers' pneumoconiosis were compared to white men in Pennsylvania (89). Croften studied bronchitis mortality in Scotland's coal mining regions and found more bronchitis as well as lung cancer among males and less bronchitis with fewer lung cancer deaths in females although their numbers were so small that this difference was insignificant (23).

Gregory studied disabling bronchitis in Sheffield, England, steel workers and discovered the interval between onset and disability was 40 years in those with onset under age 15; 10 years with onset after age 40; and 2.3 years with onset after age 60 (42). Disability was defined as loss of time from work for two consecutive winters. This is a model study of what can be done by a careful medical officer with an industrial population and should serve as an example for future studies. The degree of ventilatory insufficiency as revealed by the FEV_1/VC_p (predicted) was used by Burrows and Earles to examine survival of 200 patients with combined bronchitis and emphysema followed for five years (14). Only 30% of those with FEV_1 less than 0.21 FEV_1/VC_p survived as compared to 56% of those between 0.21 and 0.34 and 77% of those between 0.35 and 0.60. In a long-term follow-up of respiratory symptoms of 159 engineering workers studied for 11 years, Howard concluded there was a mean decrease in $FEV_{0.75}$ of 0.34 l/y and a fall in FVC of 0.64 l/y (55). Although the cigarette smokers had five times the nonsmokers prevalence of sputum production (55% vs. 11%), difference in chest illnesses was only 49% vs. 44%, and of severe illnesses, 14% vs. 11%. So the concordance between cigarette smoking, sputum production, and various chest illnesses was not very high. The $FEV_{1.0}$ was often markedly reduced by the time regular symptoms of cough and sputum production appeared (i.e., a daily sputum habit). The finding is at variance with other prospective studies which found that, in general, hypersecretion preceded dyspnea (31)(73)(91). Some subjects lost and some acquired cough and phlegm production. Breathlessness increased as defined by the limitation of walking on level ground. Bates, in a study of 216 Canadian World War II veterans from four cities over a 10-year period (1958-68), found that men with chronic phlegm and cough in middle age, who were cigarette smokers, had a mean rate of functional change and death rates similar to the population at large and that "malignant bronchitis" with dyspnea, rapid functional de-

terioration, and death was an infrequent complication of this syndrome of hypersecretion (7). Functional deterioration appeared to correlate with the numbers of cigarettes smoked. Sharp et al. studied 1,263 persons from 1961 to 1968 for respiratory symptoms and spirometric abnormalities, at the Hawthorne Works of the Western Electric Company in Chicago (105). Persistent cough and phlegm and dyspnea were about 5 times as common in cigarette smokers as in non-smokers while persistent cough and phlegm alone were only about three times more common in smokers than nonsmokers, (16% vs. 5%). Considerable numbers recovered from phlegm and sputum production. Also reversal of spirometric abnormalities was common, but it is noteworthy that the ratio $FEV_{1.0}$ to FVC remained unchanged in about 50% of both smokers and nonsmokers. Changes in FEV_1/yr or FVC/yr were not given; therefore, the ratio is meaningless. The lack of change may simply reveal that FVC and FEV_1 decreased in fixed relation to one another, preserving the original ratio. This change may be important in an aging population as strongly suggested by the study of Milne in Edinburgh (76). He found mean values of FEV_1 and FVC declined as age increased, but the decline was greater in FVC so there was a rise in FEV_1 as a percentage of FVC. Also there were changes within the population: some gained and others lost symptoms of chronic phlegm and cough. Dyspnea was less capricious and increased in 13% of the men and 7% of the women. The presence of emphysema together with cough and phlegm production (chronic bronchitis) increases the mortality and disability of a population as shown by Bates in Canadian veterans of World War II (7).

In Table V-3 several studies are summarized which include age stratified cross-sectional data (2,3,5, and 9) and prospective studies. Although there are large differences in rates of reduction in $FEV_{1.0}/yr$ at a given age in the populations studied, the rate of reduction increases with age. It is higher in those recognized as having chronic bronchitis with dyspnea (13) or chronic obstructive pulmonary disease (14)(15). An integrative summary and interpretation of such studies has been published recently by Fletcher et al. (31)(32).

The prognosis of emphysema is difficult to estimate because of the lack of agreement on clinical and diagnostic criteria, coupled with the

relative infrequency of emphysema uncomplicated by cough and phlegm production and/or CO_2 retention. Despite a literature search, prognosis data were not found. Studies of survival after respiratory failure begin at a disease stage so advanced, it is impossible to relate them to working populations. For example, the Veterans Administration Cooperative Study of Mortality (97), a study by Boushy et al. (12), and two studies by Asmundsson and Kilburn (4)(5) contain no data which is useful in this context.

DIAGNOSTIC CRITERIA

The diagnostic criteria for chronic bronchitis used by epidemiologists are cough with sputum production for at least three months of two successive years, in the absence of specific disease. These diagnostic criteria have led to the use of the term *Chronic Non-specific Pulmonary Disease* or *Lung Disease* in Europe. Because of the benign prognosis of the simple hypersecretion syndrome (previously defined) and the progressive nature of the airways obstruction syndrome which produces dyspnea on exertion and large annual decrements in function, these two syndromes should be classified separately. By so doing, the implications of separate responses or of loci or response to exposure can be defined. The presence of continuous sputum production, with or without cough, defines the hypersecretion syndrome; it does not include all those workers who have rapidly declining ventilatory function due to airways obstruction. Therefore, separate and independent criteria are needed. The most dependable is reduction in expiratory airflow in the exposed population within a time interval and at a more rapid rate than is expected for unexposed controls. Measurements of airflow must be made and repeated at two or more intervals. The population must be under surveillance using $FEV_{1.0}$ and FVC or other measurement, so that the annual decrement of function can be established. Dyspnea on exertion will usually accompany this observation, but it may not be manifested until a large loss of functional reserve and encroachment upon capacity at virtually the resting level has occurred. This takes time. Radiographic techniques including ventilatory scans using inhaled radioisotopes, bronchopulmonary lavage, and biochemical tests of secretions or serum including immunological measurements have not been shown to be useful in diagnosis.

Table V-3
A COMPARISON OF PUBLISHED DATA ON AVERAGE DECREMENTS
IN FORCED EXPIRATORY VENTILATION IN ONE SECOND (FEV_{1.0})

FEV _{1.0} Liters/Year	Reference
1. 0.052 Smokers (miners)	Higgins, I.T.T. and Oldha, P.D.: Ventilatory capacity in miners: A 5-year follow-up study. <i>Brit J Ind Med</i> 19:65-76, 1962.
0.024 Nonsmokers	Higgins, I.T.T.: Tobacco smoking, respiratory symptoms and ventilatory capacity. <i>Brit Med J</i> 1:325-329, 1959.
2. 0.025	Kory, R.C., Callahan, R., Boran, H.G., and Syner, J.C.: The Veterans Administration—Army cooperative study of pulmonary function/clinical spirometry in normal men. <i>Am J Med</i> 30:243-258, 1961.
3. 0.024	Ferris, B.G., Anderson, P.O., and Zinkmantel, R.: Prediction values for screening tests of pulmonary function. <i>Am Rev Respir Dis</i> 91:252-261, 1965.
4. 0.031	Rosenzweig, J.A., Atkins, J.A., and Schrock, L.G.: Ventilatory studies in a normal population after a seven year interval. <i>Am Rev Respir Dis</i> 94:74-77, 1966.
5. 0.026 (904) Smoking	Fletcher, C.M.: Bronchial infections and reactivity in chronic bronchitis. <i>J. Roy. Coll. Physicians, London</i> 2:183-190, 1968.
6. 0.032 Age 0.041 25-34 (756) 55-64	Higgins, I.T.T., Gilson, J.C., Ferris, B.G., Waters, M.E., Campbell, H., and Higgins, M.W.: IV Chronic respiratory disease in an industrial town: A nine-year follow-up study preliminary report. <i>Am J Pub Health</i> 58:1667-1676, 1968.
7. 0.042 Nonsmokers 0.070 Smokers 313 men age 50	Wilhelmsen, L., Orha, I., and Tibblin, G.: Decrease in ventilatory capacity between ages 50 and 54 in representative sample of Swedish men. <i>Brit Med J</i> 3:553-556, 1969.
8. 0.034	Howard, P.: A long-term follow-up of respiratory function symptoms and ventilatory function in group of working men. <i>Brit J Ind Med</i> 27:326-333, 1967.
9. 0.43 Age 0.027 25-34 0.029 35-44 0.053 45-54 55-64	Morris, J.F., Kowski, A., and Johnson, L.C.: Spirometer standards for healthy nonsmoking adults. <i>Am Rev Respir Dis</i> 103:57-67, 1971.

Establishment of work relatedness of disease depends primarily upon a careful, consistent, and complete occupational history which asks the subject to compare various symptoms at work versus at home. It is helpful in some instances to test respiratory function (usually FEV_{1.0} and FVC) after some hours of work (exposure) compared to a baseline of Monday morning after two and one-half days without work exposure. Replicable decrements in function with or following exposure provide strong support for a history of work relatedness. (Performed by competent hands they are unlikely to be biased).

In summary, only symptoms of functional impairment and measurement of impairment are sensitive for early detection of hypersecretion and of airways obstruction. There are no early physical signs, no radiological changes, and as yet no specific tests. Erosion of ventilatory reserve—which is best measured by function testing and comparison of an individual with himself across a gap of time or an exposure—is the most sensitive technique now known. Diseases which should be absent in order to make the diagnosis of chronic bronchitis are: acute reversible airways disease with or without wheezing (asthma) and acute disorders due to chemicals and living agents such as viruses and bacteria. Specific acute infections leading to pneumonia or bronchopneumonia and tuberculosis should also be differentiated. It is less important to differentiate bronchiectasis; it is probably one end stage of bronchitis characterized by dilation of airways as contrasted to fibrous distortion and obliterative loss of airways. Tuberculosis is suspected on the basis of radiographic findings in the presence of a positive tuberculin test and proven by demonstrating the causative organism in sputum (by smear and culture) or in biopsy material by a caseous necrosis with typical organisms and growth on culture. Because bronchitis is without radiographic changes by itself, the presence of radiographic changes which form part of the picture of an acute syndrome (pneumonia) or even a chronic disease (tuberculosis) can be helpful. Finally, the passage of time which allows for the therapeutic or spontaneous regression of symptoms, helps sort out disorders which are otherwise indistinguishable, including acute bronchitis. Although it would be highly desirable to have pathologic criteria for chronic bronchitis, such criteria have not been agreed upon. Includ-

ed should be: hyperplasia of bronchial mucous glands, goblet cell metaplasia and squamous metaplasia of the epithelium of large airways, and after the transition into the dyspneic phase with airways obstruction, goblet cell metaplasia with mucus obstruction in small airways.

Thus criteria applicable to bronchitis diagnosis modeled upon epidemiological criteria developed by the MRC of Great Britain have been used almost without question for two decades. Only recently, as prospective studies covering 5-12 years have been published (30)(58) (116), has the definition been challenged and suggestions made to sort out the complex association between symptoms of hypersecretion, airflow obstruction, and dyspnea—especially in relation to cigarette smoking. This approach still needs to be applied to occupational chronic bronchitis.

The well accepted diagnostic criteria for emphysema are anatomic and structural, and therefore, require examination of lung macrosections. Because lungs obtained at autopsy are far advanced in the course of the disease and cannot be used for prospective studies, other criteria must be used based upon radiographs, pulmonary function tests, and clinical changes. Of these, radiographic criteria have been most serviceable. Two out of the four major criteria of lung hyperinflation with vascular deficiency are needed to make the diagnosis of emphysema (113). In a large study of North Carolina textile workers, it was found that a retrosternal clear space greater than 2.5 cm was the most frequent finding in a working population. By itself, it was not diagnostic of emphysema, but when coupled with low flat diaphragms on either the PA or lateral film, hyperinflation was diagnosed. The presence of hypovascular zones was an additional clue for emphysema. These findings were highly correlated with dyspnea and function insufficiency, increased total lung volume, decreased diffusing capacity, and increased compliance. Finally, clinical criteria of decreased or absent breath sounds, a hyperinflated chest in the absence of bronchospasm, and reversal of hyperinflation spontaneously or by therapy make the diagnosis of advanced emphysema relatively secure. The major diagnostic confusion is due to protracted hyperinflation with airways obstruction, but without parenchymal destruction which occurs in a few individuals with asthma. They can general-

ly be identified by a family history of asthma, a greater than 15% improvement in expiratory flow rates after bronchodilators, and eosinophilia in sputum or nasal secretions. There are no biochemical or systemic manifestations of bronchitis or of emphysema that are diagnostic.

Because during the past two decades emphysema has not had generally agreed upon clinical criteria, research has been thwarted and no prospective series are available for analysis. A remedy for this unfortunate situation is to measure the total lung capacity with postero-anterior (PA) and lateral radiographs taken from a distance of 6' (44). Applied to textile workers (74) this showed their prevalence of emphysema was not above the controls. It was also used in a group of coal workers (80). Coal miners with chest radiographic evidence of pneumoconiosis (rounded densities) had larger residual volume than those without pneumoconiosis or non-mining controls. The presence of airways obstruction ($FEV_1/FVC < 70\%$) was associated with further increases in residual volume. Miners who smoked cigarettes had residual volumes from 130% to 150% of predicted. Changes in TLC were approximately 25% of those for RV.

METHODS OF PREVENTION

Since chronic bronchitis and emphysema result from the inhalation of environmental agents associated with particles, these disorders could be prevented by reducing inhalational exposures. The major exposure to reduce is main-line cigarette smoke. A possible etiologic role of viruses in chronic bronchitis, or the possibility that emphysema may be partly due to a failure of antiprotease defenses or to faulty developmental alveolarization, are not to be ignored. But without reduction of the particle burden of cigarette smoke (2 billion particles per ml, 70 billion per puff), prevention of all but the most enormous environmental exposures is likely to have a small effect upon these diseases. However, operations in many industries such as the rock digging and crushing involved in obtaining coal, ore, paving, and building material and smelting, evolved without regard to minimizing generation of dust. Such exposure was regarded only as a nuisance dust until studies showed excessive prevalences of chronic bronchitis (13). Silica and asbestiform fibers constitute a variable proportion of these dusts upon which abatement strategy should be focused. Conversion from dry to wet processing and enclosing of operations

exemplify methods to reduce particle exposures often by an order of magnitude. Environmental controls are clearly more satisfactory than respirators or other personal protection. Examples of this generalization may be: (a) the byssinosis-bronchitis in textile workers exposed to cotton, flax, and soft hemp, where the interaction of cigarette smoke and cotton dust at respirable dust levels between 0.3 and 0.9 mg/m³ appears to contribute almost equally to symptoms (74); and (b) foundry workers where the additive effect of cigarette smoke to dust containing silica is clear (24)(25). Other possible interactions between cigarette smoking and particulates would appear to be a compelling argument for dust control.

The reduction of exposure to particles is a matter for work site hygiene and must be tailored to the workplace. A suitable strategy to reduce particles frequently includes both reduction in generation of particles into the air and particle removal before being inhaled by workers. The aims are clear, but engineering and industrial hygiene assistance are essential to find the best means of air cleaning. In general, wet processing and vacuuming instead of "blowing down" are important. Filtration of air by face mask or respirator is generally less consistently applied, less effective, and more disturbing to the workers—especially during vigorous exertion, as well as being more variable and capricious than environmental measures.

Studies of lung isotope clearance suggest subjects vary in efficiency of particle removal (2)(81). Also, airways' size may control the dose which reaches the peripheral part of the lung. As airways narrow and are reduced in number, there appears to be less exposure (15). (The hypersecretion of chronic bronchitis can be looked upon as being protective.) These suppositions suggest two additional preventive measures: (1) Workers could be screened by some measure of clearance efficiency. Although at the moment this can only be done in a few laboratories, the methods are not difficult. Clearance efficiency would have to relate to responsiveness as measured by decrease in $FEV_{1.0}$ over the work shift or by some other simply performed function test. Those with good function, who would presumably be least likely to be harmed by particle exposure, could be placed in more hazardous areas. However, particle clearance may vary in individuals over time or be altered by the dust exposure itself. (2) No measures substitute for environ-

mental cleanliness, with removal of particulate burdens and vapors including gases from the work environment. However, in some special situations the air inspired by individual workers (their microenvironment) can be cleaned. Methods include respirators which filter out particles, respirators which absorb vapors, and air supply equipment which provides clean air for workers to breathe via a hood or hood and skirt arrangement in which positive pressure is maintained to exclude contaminated surrounding air. These work well in sandblasting, asbestos demolition, and chemical exposures where filtration or particle or vapor removal is difficult.

RESEARCH NEEDS: CHRONIC BRONCHITIS AND EMPHYSEMA

There is a need for data on the prevalence of chronic bronchitis and emphysema in various occupational groups. This should include groups in which a high prevalence has been found in other countries and where, because of the type of chemical agent or the severity of exposure (based on anecdotal evidence or animal experimentation), there is reason to believe that bronchitis develops. Examples would include workers involved with ammonia fertilizer; those in the petrochemical industry, where phosgene and other highly reactive compounds such as aldehydes are used as catalysts or reaction control agents; and occupations such as quarries, rock crushers, and cement and brick manufacture in which dust burdens are high. An important corollary determination is the interplay of occupational airways or lung irritation which leads to hypersecretion and to job changes by workers. High worker turnover likely conceals or prevents recognition of exposure causing chronic bronchitis.

Prospective studies are needed to establish yearly rates of functional decrement in pulmonary function; the relationship between rate of decrement in pulmonary function (such as FEV_{1.0} or flow at 50% of volume (and appearance of symptoms (sputum production and chronic cough); and then the relationship between decrement, this symptom complex, and the appearance of dyspnea and of emphysema (hyperinflation) on chest radiographs. It is especially important to determine whether they are etiologically related or just occurring together.

A problem which can be surmounted by clear definitions is differentiation of the syn-

drome of chronic cough and sputum production without dyspnea (bronchial hypersecretion) from the chronic cough and sputum production with dyspnea and airways obstruction which defines chronic bronchitis. The former does not necessarily progress to impairment, whereas the latter often leads to progressive pulmonary impairment, insufficiency, respiratory failure, and death. Because biopsies of the bronchial tree obtainable with bronchoscopy are small (particularly since the advent of fiberoptic bronchoscopy), better morphologic studies depend on material available from surgical procedures or at autopsy. Because only lungs with coexistent carcinoma are generally available for biopsy, a prospective study is needed in which the autopsy rate is sufficient to provide many lungs for careful morphologic including morphometric studies. Although the extensiveness of sampling utilized by Auerbach et al. (6) in studies of cigarette smokers is probably not required, sampling from each lung lobe, a grading system, and careful recording is needed in order to make such a study worthwhile. Enumeration of the numbers of airways, i.e., a morphometric study of numbers of branches at distal bifurcation levels, would supply knowledge concerning not only changes in airways, but the subtraction of airways by fibrous obliteration or even by failure to develop.

Studies made in the past of worker cohorts in whom PA and lateral chest radiographs were obtained could be converted into prospective studies according to the time hyperinflation appeared and its prognosis. Also, other radiographic criteria, (such as those described above) and clinical criteria could be compared. Important data concerning the natural history of hyperinflation-emphysema would be forthcoming. Careful comparisons of postmortem measurements of emphysema from lungs fixed in inflation and radiological changes show that this method could function reliably (86)(113).

The nature and degree of interaction (additive or synergistic) between occupational exposure and cigarette smoking needs to be identified. This would help establish risk profiles and provide a basis for medical surveillance for jobs where environmental controls cannot be applied.

Interactions involving particle exposure and active chemical agents—either in the particles or generated at the same or reasonably close time—should be studied.

Research must determine whether brief airways damage leads to the abrupt onset of chronic bronchitis, and whether exposure to chemical agents induces a higher attack rate of abrupt onset chronic bronchitis as a co-factor with viruses. For example, does worker exposure to phosphene (in the chemical industry) or to SO₂ (in paper pulping)—which acutely damage airways— increase the likelihood of respiratory illnesses, particularly chronic bronchitis, when viruses are widespread in the population?

Research is needed to determine to what extent and in what instances chronic bronchitis (hypersecretion) and chronic bronchitis (airways obstruction-dyspnea) are reversible disorders.

The possibility that both chronic bronchitis and emphysema have their origins in exposures of women of child bearing age (before pregnancy is recognized) should be examined. In particular, reproductive function and offspring should be studied in women who are exposed to industrial chemicals such as chelating agents in the lead, rubber, and plastics industries.

Research should be directed toward determining whether the epithelial damage of chronic bronchitis can be reversed. This might be easiest with the insidious type. If it can be reversed, e.g., by therapeutic administration of vitamin A (which is known to affect epithelial development, particularly cell differentiation), then it might be possible to forestall the connective tissue, airway obliteration, or ectasia stages of chronic bronchitis which lead to pulmonary insufficiency.

The most useful general strategy would be to have a national reporting of diseases which cause time lost from work and those causing hospitalization. This would provide much of the data needed for monitoring occupational effects on workers. Such reports could also serve as initial warning systems for new occupational illnesses not previously linked to work exposure.

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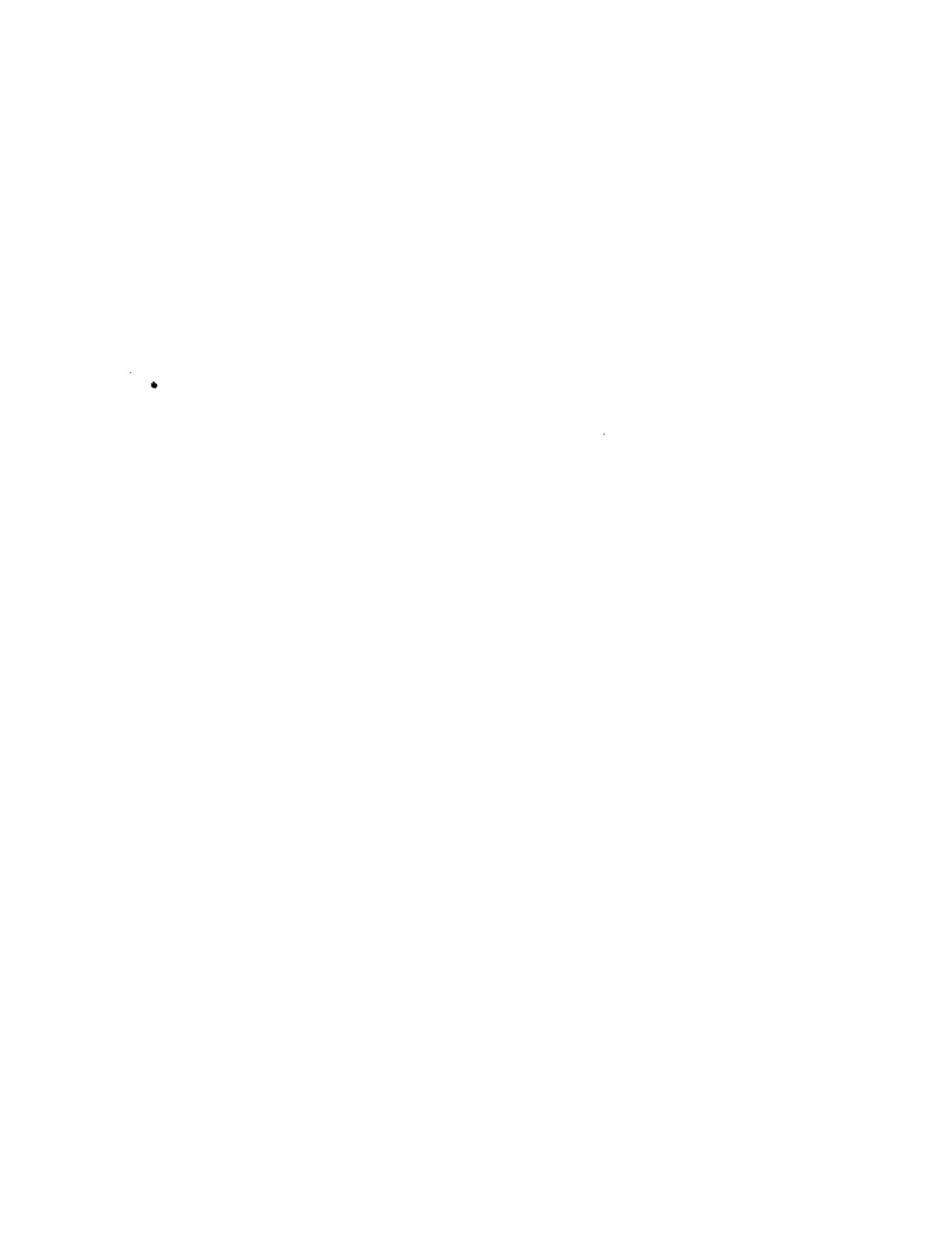
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SECTION VI
BYSSINOSIS



BYSSINOSIS

James A. Merchant

... those who hackle in the flax and hemp to prepare it for being spun and wove, afford frequent instances of the unwholesomeness of their trade; for there flies out of this matter a foul mischievous powder, that entering the lung by the mouth and throat, causes continual coughs and gradually makes way for an asthma... but at the long run if they find their affliction grows upon them they must look out for another trade; for 'tis a sordid profit that's accompanied with the destruction of health.

Bernardino Ramazzini, 1705 (142)

INTRODUCTION

Exposure to textile vegetable dusts is a major occupational hazard of global dimension. Of the three natural fibers associated with respirable dust exposure during processing, cotton (*Gossypium* species) is the predominant textile fiber, followed by flax (*Linum usitatissimum*) which is woven into linen, and soft hemp (*Cannabis sativa*), traditionally used for rope and net making, but now largely replaced by synthetic fibers.

Both developed and underdeveloped countries are dependent upon cotton as the staple of their textile economy. The U.S.S.R. leads in annual production of cotton with over 11 million bales, followed closely by the People's Republic of China and the United States. China consumes over 12 million bales annually followed by the U.S.S.R., the United States and India (52). Several underdeveloped countries are heavily dependent upon the cotton industries with significant proportions of their populations dependent upon cotton for their livelihood—Syria (16.0%), Guatemala (19.3%), Nicaragua (35.4%), Chad (71.4%) (51). With several million workers occupationally exposed to vegetable dusts worldwide, and with little evidence that cotton will be replaced by synthetic fibers, respiratory disease arising from exposure in these industries is clearly a world-wide public health problem.

DEFINITION

Byssinosis is the generic name applied to acute and chronic airways disease among those

who process cotton, flax, and hemp fibers. The acute response to dust exposure is characterized by a sensation of chest tightness upon return to exposure following a holiday or weekend break. This symptom is often accompanied by a cough, which may become productive with time, and occasionally by shortness of breath. Measurement of lung function upon return to exposure often reveals modest decreases in expiratory flow rates over the working shift. For most affected individuals, these findings will diminish or disappear on the second day of work. With prolonged exposure, both the symptoms and functional changes become more severe. Dyspnea becomes the prominent complaint while decrements in expiratory flow rates over a work shift are often marked, and clear clinical and physiological evidence of chronic obstructive lung disease emerges.

CAUSATIVE AGENTS

A great deal of interest and research has been focused on identification of the etiological agent(s) of byssinosis. The specific etiology and mechanism of this disease, however, is still not fully understood. It is generally accepted that there are three definite exposures which cause byssinosis: cotton dust (largely bract, leaf, and stem), flax dust (stem), and soft hemp dust (stem). There is some evidence that dust arising from the processing of the hard fibers, sisal (stem) and jute (stem), may occasionally result in byssinosis.

COTTON AND FLAX INDUSTRIES AND POPULATION AT RISK

Based upon 1977 Bureau of Labor Statistics figures, estimates of the total U.S. population potentially at risk to cotton dust exposure have been made (50). Taking into account all industrial processes where cotton dust exposure may occur, including over 200,000 in knitting mills where risk is considered very low, the estimated total population at potential risk is 559,700 (see Table VI-1). Perhaps half this number is significantly exposed.

It is more difficult to estimate the number of workers exposed to flax dust. The weaving of linen cloth is not a major industry in the United States, yet flax is used in a number of special textile applications. It is estimated, based upon anecdotal information, that no more than 5,000 workers are exposed. The little information available on exposure indicates that dust concentration may be marked (138). There is virtually no soft hemp, sisal, or jute processed in the United States.

EPIDEMIOLOGY

Early Observations

Observations regarding respiratory disease among those exposed to vegetable dust associated with the manufacturing of textiles began with the writings of Ramazzini. "One may see these men always covered with dust from the hemp, pasty-faced, coughing, asthmatic, and blear-eyed"(143). Following their development in Italy, textile industries flourished in France and then in England and Ireland. Shortly after the introduction of this industry to northern England, the first observations of its influence on the health of the workers were made by Jackson in 1818 (84). He observed that "... few attain their fiftieth year... there is something preys on the man thus to induce premature old age." Patissier (1822) made similar observations in France and commented that workers "must often change their work in order to prevent phthisis" (136). Thackrah, who studied the cotton textile industry in Leeds, wrote in 1831, "Workers handling cotton, as well as people working in dusty places of such plants, are not healthy as a rule. Cough and difficulties of breathing persist, and advance gradually sometimes over months, often over years" (166). J.D. Kay, also writing in 1831, observed that workers employed in the early processes were more af-

ected and that coarse cotton caused greater frequency of disease than cleaner material. He noted "... the cough is at length very frequent during the day, and continues even after its employments have ceased, disturbing the sleep, and exhausting the strength of the patient. . . . The patient is easily affected with acute bronchitis on exposure to its exciting causes, and this disease often succeeds the previous complaint." Kay further observed that symptoms are severe after returning to employment. "I have found it necessary to insist that the patient should abstain from his ordinary employment, for some time after his apparent convalescence. When this injunction has been disregarded, immediate relapse has generally followed; the most severe symptoms have reappeared"(88).

The respiratory disease suffered by textile workers was initially referred to as "tracheal phthisis" by Gerspach in 1836 (73). Credit for coining the term "byssinosis" belongs to Adrien Proust.* The term has not been used uniformly; the disease has frequently been referred to as "stripper's asthma or stripper's and grinder's asthma" (48)(49).

Mareska and Heyman studied 2,000 cotton workers in Ghent, Belgium, in 1845 and first described the periodicity of Monday chest discomfort (cited by Tuypens (168)). Greenhow (1861) also noted that symptoms were more severe at the beginning of the workweek and provided a lucid clinical picture of the disease (75).

In addition to the frequently mentioned chronic bronchitis, many of the early descriptions of workers severely affected are clinically consistent with emphysema (48). Among the signs in common with emphysema are weight loss, cough productive of only scanty amounts of sputum, wheezing respiration, and a quiet chest to auscultation.

In 1932, the British Home Office established a Departmental Committee on Dust in Cardrooms in the Cotton Industry. Its report described the disease as respiratory in nature with three stages (145): (A) The stage of irritation; (B) The stage of temporary disablement or incapacity; (C) The stage of total disablement or incapacity.

*The word byssinosis is derived from the Greek *Bvoos* or Latin *byssus*, defined by *The Shorter Oxford Dictionary*, 1962, as "an exceedingly fine and valuable textile fiber and flax, but used also of cotton, silk, etc."

Table VI-1
WORKERS EXPOSED TO COTTON DUST BY INDUSTRY SECTOR

Industry Sector/Title	Sic. No.	Exposed Workers ^a (000)
Agricultural		
Cotton ginning	0724	92.6 ^b
Classing	9641	0.3 ^c
Cotton compresses and warehouse	4221	10.8 ^d
Cottonseed oil mills	2074	4.0
Yarn Manufacturing		
Broad woven fabric mills, cotton	2211	86.6
Broad woven fabric mills, fiber, and silk ^e	2331	47.0
Circular knit fabric mills	2257	1.0
Yarn spinning mills	2281	34.4
Texturizing, throwing, twisting, and winding mills	2282	13.9
Thread Mills	2384	3.6
Tire cord and fabric	2296	1.6
Fabric Manufacturing		
Broad woven fabric mills, cotton	2211	16.2
Broad woven fabric mills, man-made fiber, and silk	2221	8.8
Narrow fabrics	2241	4.5
Knitting mills	225	200.7
Textile Waste		
Paddings and upholstery fillings	2293	4.9
Processed waste	2294	3.7
Mattresses and bedsprings	2515	<u>25.1</u>
		559.7

^aExcept as noted, the estimates of exposed workers were developed from 1977 data for production workers obtained from the Bureau of Labor Statistics.

^bDuring the 1974-75 growing season, 92,647 W-2 forms were issued (Docket exhibit No.88d—Cotton Dust Hearing, Department of Labor, 1977).

^cSource: U.S. Department of Agriculture, Raleigh, North Carolina.

^dDocket exhibit No. 95b (Cotton Dust Hearing, Department of Labor, 1977).

^eCotton-synthetic blend mills.

Source: U.S. Department of Labor (50)

Schilling, who rediscovered byssinosis when he inquired into excess cardiovascular deaths among Lancashire textile workers (152), developed a grading scheme for byssinosis based on the typical stages. It is the standard definition used in epidemiological surveys today. The grading scheme is based entirely on symptomatology (147), and has been incorporated into the British Medical Research Council Respiratory Questionnaire (109)(158):

- Grade 0 — No symptoms of chest tightness or breathlessness on Mondays.
- Grade ½ — Occasional chest tightness on Mondays, or mild symptoms such as irritation of the respiratory tract on Mondays.
- Grade 1 — Chest tightness and/or breathlessness on Mondays only.
- Grade 2 — Chest tightness and/or breathlessness on Mondays and other days.

Mortality Studies

A good deal of anecdotal information regarding mortality is available from early writings. In 1818, Jackson observed that few cotton workers "attain their fiftieth year" (84). Thackrah (1831) commented on those employed in flax rippling: "... most of the men doing this work are young. Very few of them reach the age of 30 if they stay on the job"(166). Greenhow studied workers exposed to flax and cotton dust in 1861 and found evidence of increased mortality (75). Similarly, Pardon (1873) recorded excess mortality among flax workers as compared to other classes in the community of Belfast (135). Barbero studied 100 consecutive deaths among hemp workers and compared the results with 100 consecutive deaths among farm workers from the same region in Spain for the years 1938 to 1943 (6). The mean age of death for hemp workers was 39.6 years, that for farm workers 67.6 years. Barbero found cardiorespiratory disease listed as a cause of death twice as frequently among hemp workers and noted that hemp workers aged 30 appeared to be 40 to 50.

The most complete mortality data for those exposed to cotton dust is found in the Decennial Supplements to the Annual Report of the Registrar General of Births, Deaths, and Marriages in England and Wales between the years 1880 and 1932. Caminita reviewed these reports and found (excluding pulmonary tuberculosis) an in-

creased mortality from respiratory disease, particularly bronchitis and pneumonia (40). Later reports emphasized that the excess mortality from respiratory disease occurred chiefly among cardroom and blowing room operatives and strippers and grinders, rather than other cotton workers.

Schilling reanalyzed the Registrar General data between 1910 and 1932 (154)(155). All showed excess mortality from respiratory and cardiovascular causes among strippers and grinders over age 55 compared with cotton operatives and all males over that age. Schilling was able to explain the excess cardiovascular deaths by showing that a substantial proportion of cardiovascular deaths should have been classified as respiratory deaths. They were not because, with multiple certification, cardiovascular and renal disease was given preference over respiratory disease as cause of death prior to 1939. He concluded that "mortality from byssinosis has been underestimated in the past"(152).

Mortality data among textile workers in the United States is limited. Clark and Gage reported mortality by cause of death for communities in Massachusetts for the years 1896 to 1910 (47). They found 111% as many deaths from tuberculosis and 163% as many deaths from pneumonia and bronchitis in cotton mill communities as compared to shoe manufacturing communities.

More contemporary studies of cotton textile workers' mortality have not revealed consistent excesses in overall mortality. Assessment of respiratory mortality has been difficult because of a lack of adequate work history data in one study (62) and relatively small cohorts in two other studies (53)(132). Enterline studied 6,281 white male textile workers employed in Georgia mills (62). He found their overall mortality experience was similar to that of asbestos building product workers and asbestos friction material workers, while that for asbestos textile workers was clearly increased. There was, however, no evidence of excess respiratory disease deaths among all cotton workers, when cause-specific rates were compared to U.S. white male mortality rates. Daum investigated a cohort consisting of a South Carolina local union membership employed between 1943 and 1949 (53). Initially, these mills processed cotton, but later a cotton synthetic blend. In this small cohort, moderate increases in respiratory deaths were found among male carders with 10 to 20 years of exposure and

among female spinning room workers with greater than 20 years of exposure. Evidence of self-selection out of mill work by those with poorer health was noted. Similarly, a recent mortality study of two mills in North Carolina found a trend toward an increase in respiratory mortality with increasing duration of exposure, but no overall increase in respiratory mortality (132). These authors also reported some significant increases in cardiovascular mortality and suggested methodological considerations which may in part explain these findings.

Morbidity Studies

Probably the first epidemiological study of morbidity among textile workers was conducted by Jackson in 1818 (84). As indicators he used sickness compensation and a control population of nontextile members of "Sick-Societies." "From the aggregate of ten extensive cotton-factories, the workmen [who are members of Sick-Societies] have received, upon an average . . . the relief to the amount of 11 s 6 d each per annum; other mechanics, &c. to the amount of 4 s each, per annum." Mareska and Heyman (1845) (as cited by Caminita (40)) studied 1,000 male and 1,000 female cotton workers with respect to occupational, economic, and social factors and were perhaps the first to measure dust levels. They found hospital admissions for pulmonary afflictions twice as frequent among cotton workers as other workers. Malcomb (1856) studied 2,078 flax workers in Belfast and found 12.1% of 262 preparers, 4.1% of 1,281 spinners, 0.9% of 457 reelers and 0.8% of 78 weavers to have diseases of the chest (104). Edgar Collis studied 126 strippers and grinders exposed to three grades of cotton by three stages of severity (48). Those exposed to coarse cotton were most frequently (91.3%) and most severely (56%) affected; those exposed to fine cotton were affected least often (61.9%) and had the lowest prevalence of severely affected workers (28.5%). Bradford Hill compared the incidence of illness among strippers and grinders with that of warehousemen and ringroom workers from 1923-27 (79). For disease other than respiratory there was little difference in rates, but after the age of 30, the rate for strippers and grinders was two to three times that for warehousemen and ringroom workers, exposed to less dusty areas. In the United States in 1933, Britten and colleagues found cotton workers to be

underweight and to have reduced vital capacities and chest expansion. Carders had over double the sickness rate found in spinners (38).

Schilling's studies of the Lancashire cotton textile industry (reported in 1951 and 1952) heralded a new era of inquiry into respiratory disease among textile workers (154)(155). Although he was primarily concerned with increased cardiovascular mortality, his surveys of Lancashire mills revealed that respiratory disease, specifically byssinosis, was the major health hazard. He initially studied 131 carding and blow room workers and classified their complaints into three grades of byssinosis: 66% were found to have Monday chest tightness (Grade 1); 11% were judged, in addition, to have some permanent disability with effort intolerance when not at work (Grade 3) (155). In 1955, Schilling extended his observations of cardroom operatives to ringroom workers and male spinners which he found to have byssinosis prevalence rates of 4% and 12%, respectively (157). He and his colleagues tested the reliability of his questionnaire and found that two observers agreed as to byssinosis grade in 14% of the subjects, but disagreed as to the presence or absence of byssinosis in only 7% (156). The grading scheme was then validated by studying "indirect" maximum voluntary ventilation (MVV). Progressively higher grades of byssinosis were found to have progressively lower MVV's when compared to nonexposed controls and exposed nonbyssinotics.

Since this study, ventilatory function has been used widely in epidemiological surveys of vegetable dust exposure, most notably by McKerrow and colleagues who first demonstrated that workers grouped by progressively higher grades of byssinosis could be expected to have progressively greater decrements in expiratory flow rate on Mondays thereby providing an independent validation of Schilling's grading scheme (98). Following these studies by Schilling and McKerrow, investigations have been made into the respiratory effects of a variety of vegetable dusts under many work conditions in countries around the world. Indices of health effects have most commonly included the prevalence of byssinosis, the prevalence of chronic cough and phlegm or chronic bronchitis, the prevalence of weekend dyspnea, and measures of ventilatory capacity. Risk factors including level of dust exposure, smoking, duration of dust exposure, air pollution, age, and sex have been examined and

will be reviewed in the following pages.

Indices of Health Effects

Byssinosis Prevalence, Cotton

The greatest number of morbidity surveys have been carried out in the cotton textile industry, where byssinosis has been found to be most prevalent. Recent epidemiological studies of byssinosis prevalence began with Schilling's Lancashire study of 1955 (see Table VI-2). A strikingly high prevalence of Grade 1 and 2 byssinosis was found, especially among those in dustier jobs. Subsequent British surveys have established that byssinosis occurs among spinners (68) (110) and winders and among those who work with waste cotton (54). Similar observations have been made in prevalence surveys in other countries (see Table VI-2).

Studies of textile workers in the United States did not begin until after 1960 when McKerrrow and Schilling visited cotton mills in Alabama where they found some workers with histories typical of byssinosis (101). In 1965, Heaphy and Kilburn studied 10 hospitalized patients with previous cotton exposure and characteristic histories of byssinosis (78). In 1967, Bouhuys and associates studied 22 southern textile workers with chronic respiratory disease and found 14 to have histories consistent with byssinosis (26). Epidemiological studies of the U.S. textile industry began with two studies conducted in 1967 by Schrag and Gullet (159) and by Bouhuys and associates (36) (see Table VI-3). Since then, several other prevalence surveys have been completed, including two reporting the results of company-wide surveillance programs. When results are categorized by work area, similar byssinosis prevalence patterns are observed among these studies (see Table VI-3).

Several inquiries have been made into cotton dust exposure in processes other than those directly dealing with the manufacturing of textiles. Batawi, in two surveys, found 28.4% and 33% of Egyptian cotton gin workers to have symptoms typical of byssinosis (8)(11). Two cotton seed pressing plants were also investigated and 52.6% found to be affected. Gilson reported decreased expiratory flow rates among workers in Ugandan cotton gins (74). Khogali studied 323 cotton gin workers in the Sudan and found 20.0% with byssinosis; among 35 workers in the farfara process, the prevalence was 48.6% (89).

Kondakis studied 70 gin workers in Greece exposed to low levels of cotton dust (91). He found no typical case of byssinosis but evidence of "subclinical" effects of cotton dust on pulmonary function. Palmer and colleagues studied 203 U.S. gin workers and 260 controls and found no cases of byssinosis by questionnaire, but did find evidence of greater functional impairment among ginners as determined by spirometric testing (134). Noweir studied 147 employees of two Egyptian cottonseed oil extraction plants and found 30% of the 110 exposed to cotton dust in the delinting operation to have byssinosis, while no such diagnosis could be made among the 37 working in the oil extraction (130). Similarly, Simpson has reported significant biological activity as judged by decrement in expiratory flow among those in the Australian delinting and garnetting industries (161)(162). Jones and colleagues studied 172 workers in 4 U.S. cottonseed mills (86). Just over 2% were found to have byssinosis while a greater prevalence of functional abnormalities was observed.

Byssinosis Prevalence, Flax

Several studies of flax workers have been reported with results similar to those exposed to cotton dust. Mair and colleagues studied the Dundee textile industry where they found 15.7% of 242 flax workers to have mild symptoms of byssinosis (102). Bouhuys studied small populations of flax workers in the Netherlands and reported byssinosis in 67% of those exposed to biologically retted flax; those exposed to dust from chemically retted flax had no byssinosis (25)(35). Batawi and Hussein conducted a random survey of family heads in an Egyptian village where they found 92.5% of those who beat flax in their home, 75% of those who worked regularly in the plant, and 48.4% overall had typical byssinosis; 2.6% were judged to be disabled (10). Ferris and colleagues studied 161 flax mill workers in New England and found no typical cases of byssinosis, but did find an increase in nonspecific lung disease (65).

A small cross-sectional study of flax dust exposure at a paper manufacturing plant in North Carolina, however, revealed 3 of 27 exposed workers to have Monday chest tightness, together with significant declines in expiratory flow rates among those with high dust exposure (138). The most extensive flax survey was conducted in Northern Ireland (41)(60)(61). The

Table VI-2
BYSSINOSIS PREVALENCE
SELECTED STUDIES OF COTTON TEXTILE WORKERS

<i>Year</i>	<i>Investigator</i>	<i>Industry Process</i>	<i>Prevalence</i>	<i>Notes</i>
<i>Great Britain</i>				
1955	Schilling (157)	Carders/Setters/Fitters	42.5	Grade 1 & 2
		Strippers/Grinders/Blowroom	65.3	"
1960	Roach & Schilling (147)	Coarse Mills		
		Cardroom		
		Men	63.0	Grade ½ & 1 & 2
		Women	48.0	"
		Spinning Rooms		
		Men	11.0	"
		Women	1.0	"
		Fine Mills		
		Men	7.0	"
		Women	6.0	"
1964	Lammers (94)	Lancashire Mills		
		Cardroom	13.5	Fine Mills
		Spinning	1.5	"
		Dutch Mills		
		Cardroom	17.0	"
		Spinning	1.6	"
1966	Dingwall-Fordyce (54)	Waste Cotton	30.0	Grade ½ & 1 & 2
		Raw Cotton	62.0	"
1967	Mekky (110)	Winders		
		Men	13.8	Grade ½ & 1 & 2
		Women	18.8	"
1970	Molyneux & Tombleson (123)	Cotton		
		Men	78.3	Grade ½ & 1 & 2
		Women	25.6	in 10 occupations
		Man-Made Fiber		
		Men	4.1	All had previous
		Women	4.6	cotton dust exposure
1973	Fox (68)	Blow and Cardroom	83.8	Men-Grade ½ & 1 & 2
		Ring Spinning	5.5	M & F "
		Winding	13.4	M & F "
<i>Belgium</i>				
	Tuypens (168)	Cotton Workers	11.0	
		Severely affected	1.0	

Table VI-2
BYSSINOSIS PREVALENCE
SELECTED STUDIES OF COTTON TEXTILE WORKERS (Continued)

<i>Year</i>	<i>Investigator</i>	<i>Industry Process</i>	<i>Prevalence</i>	<i>Notes</i>
<i>Egypt</i>				
1962	El Batawi (8)	Carders	26.6	
1964	El Batawi & Shash (11)	Strippers and Grinders Waste Cotton Washed Cotton	35.7 26.7	
1964	El Batawi (11)	Blow Room Cardroom	18.0 43.0	
<i>Sweden</i>				
1965	Belin (13)	Carders in Four Mills	25-60%	
<i>Australia</i>				
1965	Gandevia & Milne (72)	Cotton Operatives	14%	Mild symptoms
<i>India</i>				
1966	Siddhu (160)		9%	
1967	Viswanathan (177)		8.4%	
<i>Yugoslavia</i>				
1971	Valich & Zuskin	Women Cotton	21.0	Nonsmokers
1972	(171)(173)	Operatives	88.3	Nonsmokers

study included 3,052 workers over the age of 35 and exposed primarily to flax, although other fibers were considered as well. Pre-preparers were found to be most frequently affected (54.1%), followed by preparers (26.6%), finishers (1.8%), others (4.2%), and wet finishers (0.5%). Valic and Zuskin studied 30 nonsmoking women flax workers in Yugoslavia and found 30% to have typical histories of byssinosis (173).

Byssinosis Prevalence, Soft Hemp

Fewer studies have been conducted in mills processing hemp, but results are similar to those for cotton and flax. Barbero and Flores described chronic respiratory disease among Spanish hemp workers (6) who were further studied by Bouhuys and colleagues (22). Seventy-seven percent of the male workers in one plant and 33% of males in a second plant were found to have histories typical of byssinosis. Twenty retired hemp workers were examined and 80% found to have far advanced byssinosis. In a later study, 91% of those workers over the age of 50 gave a history

of Monday dyspnea (23). Valic et al. studied hemp workers in Yugoslavia and found 40.6% to be affected by byssinosis (174). During that study, three of the investigators developed byssinosis symptoms associated with reductions in expiratory flow rates. In a later study, Valic and Zuskin reported a byssinosis prevalence of 39% among 102 nonsmoking women exposed to soft hemp dust (173).

Byssinosis Prevalence, Rope, Sisal, and Jute

It is now recognized that exposure to dust during the manufacturing of rope and other products from the hard fibers of sisal and jute is rarely associated with typical byssinosis but can result in decreases in ventilatory function and symptoms of nonspecific respiratory disease. McKerrow et al. studied 44 workers exposed to vegetable dusts of Manila and St. Helena hems and sisal used to make rope; no byssinosis was found but moderate and significant falls in FEV_{1.0} and FVC were found (99). Munt et al. studied 82 workers who were manufacturing rope from the

Table VI-3
BYSSINOSIS PREVALENCE
UNITED STATES STUDIES OF BYSSINOSIS PREVALENCE

<i>Year</i>	<i>Investigator</i>	<i>Industry</i>	<i>N</i>	<i>Prevalence</i>	<i>Notes</i>
1968	Bouhuys (36)	Cotton Mill Carders Spinners	214	26 29	Many exposed less than one year
1968	Schrag & Gullet (159)	Cotton Mill All Studied Carding Spinning Winding Weaving	509	12 29 10 13 10	
1969	Zuskin (182)	Cotton Mill Carders Spinners	59 99	25 12	
1970	Merchant (114)	Cotton/Synthetic Carders Other Jobs	441	20 2	Grade 1 & 2 " "
1973	Merchant (118)	Cotton Mills Preparation Men Yarn Processing Men Women Slash/Weave Men Women Cotton/Synthetic Preparation Men Women Yarn Processing Men Women Slash/Weave Men Women Synthetic/Wool Men Women	208 231 208 224 140 142 21 103 246 87 65 433 433	38.4 12.9 15.9 15.4 11.1 21.9 16.8 2.1 6.5 6.7 4.5 1.1 0.0	Grade ½ & 1 & 2 "
1973	Braun (37)	18 Cotton Mills Carders Noncarders	611 284	21.7 5.4	"Any Tightness" "
1973	Imbus (82)	Company Wide Surveillance Program Cotton Preparation Cotton/Synthetic Spinning	10,133	4.6 26.2 2.0	Grade ½ & 1 & 2 " "

Table VI-3
BYSSINOSIS PREVALENCE
UNITED STATES STUDIES OF BYSSINOSIS PREVALENCE (Continued)

<i>Year</i>	<i>Investigator</i>	<i>Industry</i>	<i>N</i>	<i>Prevalence</i>	<i>Notes</i>
		Winding		2.0	"
		Twisting		2.0	"
1976	Martin & Higgins (105)	Company Wide Surveillance Program	6,631	3.0	Grade ½ & 1
		Preparation	661	15.9	"
		Yarn Processing	1,284	1.4	"
		Weave/Other	3,443	1.1	"

same fibers (127). Although no byssinosis was found, rope workers had significantly more nonspecific chest tightness than controls and small drops in expiratory flow. In another study in which rope workers were exposed to flax (35%) and soft hemp (65%) dusts, symptoms of byssinosis were found in 10% of all studied and 37.5% of those in high dust areas (163).

Mair et al. reported no evidence of byssinosis, increased bronchitis prevalence or decreased ventilatory capacity in jute workers compared with controls (102). Gilson et al. studied workers in a Kenya sisal factory and an English jute mill and found little evidence of biological activity based on measurement of expiratory flow over a work shift (74). In this study, in which cotton was also considered, the authors suggested the order of biological dust activity, from greatest to least, was cotton > flax > sisal > jute. Valic and Zuskin studied five groups of nonsmoking women (173). Each group was exposed to a separate vegetable dust. Duration of exposure to dust was controlled; total dust levels were less well controlled and ranged between 16.23 (hemp) and 1.92 (sisal) mg/m³ for the five groups (respirable levels were not available for all groups). Based on this study—in which significant decrements in expiratory flow but no cases of byssinosis were found among sisal and jute workers—Valic and Zuskin concluded the proper order of biological activity was soft hemp > flax > cotton > sisal > jute. Further studies of sisal workers confirmed these observations for this dust exposure (164) (180). Similarly, Gandevia and Milne, who studied 46 men exposed to sisal dust in the Australian felt and wadding industry, found no typical byssinosis but did find a productive cough

to be common, particularly among smokers (72).

Chronic Cough and Phlegm, Chronic Bronchitis Prevalence

Increased rates of chronic cough, phlegm, and chronic bronchitis have been repeatedly observed among workers exposed to high dust levels and those with symptoms typical of byssinosis. Most surveys have used the British Medical Research Council respiratory disease questionnaire (109) to identify workers with cough and phlegm and those with bronchitis, (usually defined as the production of phlegm on most days for at least three months out of a year). Because nearly all surveys in the textile industry have been cross-sectional, conditions defined via a time factor are necessarily more affected by outward migration than conditions such as byssinosis which are strongly associated with current dust levels (60)(114). Other risk factors, such as age and smoking (known to be important in chronic bronchitis), must also be considered and have frequently made interpretation of data difficult, particularly in small populations.

Because initial surveys were conducted in the Lancashire area where chronic bronchitis is common, possible associations between cotton dust exposure, cigarette smoking, air pollution, byssinosis, and chronic bronchitis were of particular interest. To assess the role of climate and air pollution in contributing to respiratory disease among cotton workers, Lammers and colleagues studied Lancashire and Dutch cotton workers with similar cotton dust and tobacco smoke exposure (94). The prevalence of byssinosis between the two areas was similar, but a

clear excess of chronic bronchitis was observed among English workers and was attributed to atmospheric pollution. This study also suggested that chronic bronchitis *per se* does not influence the prevalence of byssinosis. Gilson studied textile workers in Africa where chronic bronchitis is uncommon. He found evidence suggestive of byssinosis, and concluded that chronic bronchitis is not necessarily associated with early stages of byssinosis (74). Batawi studied cotton gin workers in Egypt and found no more chronic bronchitis among those exposed to cotton than among controls despite a byssinosis prevalence of 38.4% among the gin workers (8). He concluded that there was no necessary link between byssinosis and chronic bronchitis, but differences in smoking habits between the two populations could not be ruled out. Similarly, Mair and colleagues found no increase in bronchitis prevalence among flax workers when compared to controls, but found that flax workers smoked less and suggested that flax exposure may discourage smoking (99)(102). Gandevia and Milne found 8% of their 50 cotton workers to have bronchitis—considered low for Australia (71). However, based on the pattern of expiratory flow over a workweek, they concluded it was likely that there was a closer association between byssinosis and chronic bronchitis than generally appreciated.

Review of other surveys tend to support this concept. Several surveys of cotton processes have reported elevated rates of chronic cough and phlegm or chronic bronchitis among those with heavy cotton dust exposure compared to those with lesser exposure or control subjects (89)(159)(173)(182). Others have examined the prevalence of bronchitis among cotton workers with symptoms of byssinosis and have found a uniformly strong association in addition to an increased bronchitis prevalence among those at risk (36)(68)(82)(114)(119)(123). Similar observations have been made in the well-controlled studies of flax workers in Northern Ireland (41)(60)(61). Studies of those exposed to hemp provide further evidence of the frequency of bronchitis in these populations. Bouhuys found chronic bronchitis to be particularly common among retired hemp workers (22)(23). Valic found a significant association between chronic bronchitis and byssinosis, but not between the severity of the two conditions (174). Studies of workers exposed to Manila and St. Helena hemp, sisal, and jute have

revealed no convincing evidence that chronic cough and phlegm is more common than would be expected in inert dust exposure. Mair found no increase in bronchitis in jute workers compared with controls (102). Similar conclusions have been reached in other studies of hard fibers (127)(171)(173)(180). Gandevia and Milne concluded that productive cough among jute workers was most closely associated with smoking (72).

Dyspnea Prevalence

Indices of dyspnea have been less frequently considered in cross-sectional surveys, perhaps because as a late manifestation of respiratory disease, it is more likely to be influenced by selection and outward migration. Like bronchitis, assessment of dyspnea has most often depended upon the MRC questionnaire of respiratory symptoms (which provides increasing grades of severity for shortness of breath on the weekend when away from exposure). Using this approach, Elwood reported a marked association between dustier occupational groups and increased dyspnea grade, as well as a significant increase in shortness of breath, among those with Grade two and three byssinosis (61). Bouhuys et al. found significantly more dyspnea among hemp workers than control farm workers and also found dyspnea to be a common finding in retired hemp workers (22)(23). Valic and Zuskin have found increased dyspnea prevalence consistently in their studies of nonsmoking Yugoslavian women (171)(172)(173)(179).

United States surveys of cotton mills have also found increased dyspnea prevalence among byssinotics (36)(114)(159) and among carders compared with spinners (182). An indirect indication of dyspnea among American textile workers is the Social Security proportional morbidity ratio for emphysema, chronic bronchitis, and other respiratory diseases, exclusive of tuberculosis and cancer. Ratios of 1.40 to 2.22 have been quoted for male and female textile workers under age 65 relative to all workers for the period 1959 to 1962 (H.E. Ayer, as cited by Zuskin (182)). Similar ratios, particularly for U.S. textiles workers in preparation areas, have been observed upon recent review of this data (131).

Ventilatory Function Tests

Like other indices, studies of ventilatory function have been done primarily among survivor populations as represented in cross-sectional

studies. Retirement due to disability among female cotton textile workers in Finland has shown a slight increase in disability due to respiratory diseases with evidence of selection out of employment prior to pensionable disability (92). A variety of pulmonary function parameters have been used and will be considered more completely in the section dealing with physiological aspects of vegetable dust exposure. The tests most commonly used in epidemiological studies have been measures of expiratory obstruction—initially the $FEV_{0.75}$ and its derivative, the indirect maximal breathing capacity (IMBC), and later the $FEV_{1.0}$ together with FVC. Two major effects of vegetable dusts on ventilation have been consistent. The first is a chronic effect characterized by airways obstruction with reduction in $FEV_{1.0}$, FVC, and the $FEV_{1.0}/FVC$ ratio. The second one is an acute effect characterized by significant airways obstruction developing over a few hours of dust exposure, particularly following an absence from exposure of two or more days.

The chronic effect of vegetable dust exposure has most often been judged by measuring pulmonary function prior to work on Monday, at which time any persisting acute effects have been dissipated. Decreased rates of expiratory flow and FVC have been consistent findings in those with byssinosis compared to those without byssinosis; in those with heavy vegetable dust exposure compared to those with no dust exposure; and in those who smoke compared to those who do not. Cross-sectional studies have, however, resulted in some paradoxical observations. Bouhuys and colleagues reported significantly higher $FEV_{1.0}$ levels among active 50 to 60-year-old hemp workers who were moderate to heavy smokers compared with those who were nonsmokers or light smokers of the same age and exposure (32). Twenty-six percent of the hemp workers were former smokers; self selection was probably responsible for this unexpected observation.

Schilling et al. first observed that workers with typical symptoms of byssinosis had lower expiratory flow rates than those without Monday symptoms (157). This observation has been confirmed by several investigators (11)(22)(23)(43) (159). Zuskin and Valic reported chronic changes in ventilatory capacity occurred primarily in workers with a history of byssinosis with prolonged dust exposure, as opposed to those with

byssinosis but short exposure to vegetable dust (179). Others have also found expiratory flow rates to be reduced among byssinotics and, in addition, have reported that chronic cough and phlegm, together with Monday chest tightness, can be expected to result in a further lowering of pulmonary function (82)(94)(174). Although the size of study populations has precluded controlling for smoking habit in some of these studies, Imbus and Suh studied a population large enough to categorize by smoking habit and sex (82). Among nonsmoking men and women and smoking women, those with byssinosis and bronchitis had lower mean $FEV_{1.0}$ levels than byssinotics alone. Those with byssinosis had lower $FEV_{1.0}$ levels than those with bronchitis alone, and the latter had lower levels than those with neither condition. Among male smokers, the order was the same with the exception of those with byssinosis alone and those with bronchitis alone who had the same mean $FEV_{1.0}$. Those exposed to high concentrations of respirable dusts, particularly those working in preparation work areas, have been found to have lower levels of ventilatory capacity. Carey and colleagues found that byssinotic preparers had lower mean $FEV_{1.0}$ and FVC levels than nonbyssinotic preparers and nonpreparers independent of age, height, and smoking (43). They also found that nonbyssinotic preparers had a lower $FEV_{1.0}$ than nonbyssinotic nonpreparers. Bouhuys found significantly reduced flow rates among populations exposed to cotton (21), flax (35), and hemp (22)(23) than nonexposed control groups. Batawi and colleagues, studying workers exposed to cotton dust in Egypt, found those with heavy dust exposure had the lowest flow rates; unexposed controls had the highest (11). Merchant and colleagues found reduced $FEV_{1.0}$ and FVC occurred particularly among current smokers exposed to higher dust levels (114)(117).

McKerrow et al. first observed the acute reduction in expiratory flow. It was most marked after an absence from exposure, among those with higher grades of byssinosis, and among those exposed to higher dust levels (98). Based on these observations, they suggested that symptoms of Monday chest tightness and dyspnea might be explained by the rate of reduction in flow—a hypothesis that has been questioned by others because the degree of reduction, although significant in grouped data, is often not marked (12). Others have confirmed the finding that

Table VI-4
RECOMMENDATIONS FOR CLASSIFICATION AND MANAGEMENT
OF WORKERS EXPOSED TO COTTON DUST

Functional Severity	FEV 1* (% of predicted)	FEV 1** (%)	Interpretation of FEV 1	Recommendations for Employment
F0	>80 (No evidence of chronic ventilation impairment)	(a) -4 to 0; or more	(a) Minimal or no acute effect of dust on ventilatory capacity	No change; annual FEV 1, and questionnaire
		(b) -9 to -5 or more	(b) Moderate acute effect of dust on ventilatory capacity	No change; 6 mo. FEV 1, and questionnaire
		(c) -10 or more	(c) Definite and marked acute effect of dust on ventilatory capacity	Move to lower risk area; 6 mo. FEV 1, and questionnaire
F1	60-79 (Evidence of slight to moderate irreversible impairment of ventilatory capacity)	(a) -4 to 0; or more	As (a) above	No change; 6 mo. FEV 1, and questionnaire
		(b) -5 or more	As (b) above	Move to lower risk area; 6 mo. FEV 1, and questionnaire
F2	<60 (Evidence of moderate to severe irreversible impairment of ventilatory capacity)	—	—	Work requiring no cotton dust exposure, detailed pulmonary examination, and questionnaire

*FEV 1 in absence of dust exposure (2 days or longer).

**Difference between FEV 1 before and after 6+ hours of cotton dust exposure on a first working day.

Derived from Organizing Committee of National Conference on Cotton Dust and Health, (133).

Source: National Institute for Occupational Safety and Health (128).

those with higher grades of byssinosis, when categorized, have the greatest reduction in expiratory flow (35)(41)(42)(71)(113). Bronchitics and byssinotics tend to have greater decrements in expiratory flow than those with byssinosis or bronchitis alone (82)(174). Based upon the association between byssinosis grade and decrease in expiratory flow, Bouhuys first proposed a functional grading scheme for byssinosis (later modified—see Table VI-4) (133) which employed both pre-exposed $FEV_{1.0}$ and decreased $FEV_{1.0}$; exposure was defined as significant if greater than 200 cc (24). Subsequent reports have shown that in individual cases the relationship between Monday fall, when so defined, and byssinosis is not strong: an appreciable proportion of non-byssinotics have a large Monday decrement while many byssinotics do not show a significant decline (12)(82)(123).

Because expiratory flow can be easily measured in untrained subjects and provides an objective indicator of biological effect, it has been widely used to assess the degree of biological effect in populations exposed to vegetable dusts (7)(22)(23)(36)(82)(114)(117). Those exposed to cotton, soft hemp dust, and flax usually have greater decrements in expiratory flow than those exposed to similar dust levels from hard fibers (74)(172). Those exposed to higher dust levels consistently been found to have more marked decrements in expiratory flow; a linear dose response relationship has also been described (11)(115)(118). Based on decrements in expiratory flow among those who smoked heavily and were exposed to moderately high concentrations of cotton dust, McKerrow and Schilling suggested that heavy smoking may potentiate the flow rate response (101). Imbus and Suh reported no greater decrement in $FEV_{1.0}$ among smokers than nonsmokers, but Merchant et al. found significant reductions in $FEV_{1.0}$ and FVC occurred only in smokers with no significant reduction in flow among nonsmokers (117).

Three prospective studies have considered reduction in $FEV_{1.0}$ over time (14)(116)(172). In each of these studies, conclusions were based upon a survivor population with attrition of the original population exceeding 25%. In addition, variance of annual decline measurements has been found to exceed the decline itself (16). A study of 28 workers exposed to fine cotton in Yugoslavian mills over a nine-year period revealed

no greater decline than would be expected for aging alone (172). Berry et al. reported roughly twice the annual decline among cotton workers than occurred among those working with synthetic fibers (14). The decline attributable to cotton dust exposure was slightly greater but similar to that attributable to smoking. The authors found no evidence of a greater decline among survivors with a history of byssinosis, but they did find some evidence of greater annual declines among those in dustier work areas and among those exposed for 0-4 years, compared to those exposed over a longer period. Merchant and colleagues similarly found workers, many of whom were new employees, exposed to high levels of cotton dust had annual declines greater (>200 cc/yr) than those exposed to lower dust levels (>60 cc/yr), but who also had a longer duration of dust exposure (116). Zorach studied workers before employment and following several weeks of exposure in a dusty cotton mill and found pre-shift $FEV_{1.0}$ declines in excess of 10% were not uncommon (personal communication).

Estimation of Risk

Estimation of respiratory disease risk among those exposed to vegetable dust and identification of factors which predictably influence risk has been limited by the type of data available. No prospective study has been completed that was not greatly affected by high rates of outward migration—leaving a survivor population from which to estimate risk. Available data is largely cross-sectional which necessarily affects risk estimations and may differentially affect risk, depending upon the indicator utilized. Indicators of biological effect expected to be least affected are byssinosis prevalence and change in expiratory flow rate over a work shift, both of which are strongly associated with current dust levels. Indices such as cough, sputum, and ventilatory capacity before exposure (which are more affected by duration of dust exposure) are expected to be less accurate indicators of risk since more outward migration from high risk areas often occurs (32)(60)(114)(147). Indices such as dyspnea, although most relevant to impairment and disability, represent late manifestations of respiratory disease. Hence, they are poorer indicators of biological effect because of their long developmental period, over which outward migration may occur. Consequently, risk

estimations have depended on parameters which provide the best correlation with current working conditions, byssinosis prevalences, and changes in expiratory flow rates over a work shift.

Dust Concentration

There are strong *a priori* reasons for suspecting a predictable dose-response relationship of byssinosis to dust exposure. Roach and Schilling were the first to relate byssinosis prevalence to dust quantity (147). They studied cardrooms and spinning rooms in mills processing coarse and fine cotton and measured three fractions of dust: a fine fraction below $7\ \mu$ in aerodynamic diameter, a medium fraction measuring $7\ \mu$ to 2 mm in size, and total lint and dust. They further determined levels of the three main constituents of dust (cellulose, protein, and ash) and computed correlation coefficients by dust levels and constituents of cotton dust. A strong linear association between byssinosis prevalence and total dust ($r = .93$) was found; they suggested a reasonably safe level of dust exposure was 1.0 mg/m³ total lint and dust. Batawi studied four groups of cardroom workers in Egyptian cotton mills and found a strong linear association between total dust and decrement in expiratory flow over a working shift ($r = .95$) which supported the suggested safe total dust level of 1 mg/m³ (11). Elwood and colleagues in their study of flax operatives, considered the relationship between dust level and byssinosis and bronchitis prevalence among preparers over a relatively narrow range of dust exposure. These authors combined men and women exposed to flax alone or exposed to flax with synthetic fibers and found significant association between dust level and byssinosis prevalence, which was more marked with the respirable fraction of dust (60). The absence of a significant association between dust level and bronchitis prevalence was attributed to the confined range of dust exposure, factors related to the definition of bronchitis, its multifactorial etiology, and the opportunity for outward migration in the study population. Because a marked and significant association had been found between bronchitis prevalence and occupational group, the investigators concluded the relationship between dust exposure and byssinosis and chronic bronchitis differ in degree but probably not in nature (60).

Molyneux and Berry developed dose-re-

sponse relationships between dust exposure and byssinosis prevalence, simple bronchitis among nonsmokers, and Monday cough among non-byssinotic, nonsmokers (122). All showed strong linear associations with cotton dust, but only Monday cough appeared to have a true threshold (0.2-0.4 mg/m³ respirable dust—modified Hexhlet). Their data further suggested that respirable and medium fractions of dust had greater biological significance than previously appreciated. Others also observed that total dust levels, particularly in areas such as spinning and winding where higher concentrations of lint were found, did not correlate with the decrease in byssinosis prevalence (114). As a result, the vertical elutriator cotton dust sampler was developed and has been found to be a reasonable method to sample a biologically active fraction of cotton dust $15\ \mu$ and less in aerodynamic diameter (95). Studies of American cotton textile workers, in which this sampling method was used, resulted in strong linear associations between lint-free cotton dust and prevalence of byssinosis and decrement in FEV_{1.0} over six hours of dust exposure (118). Separate dose-response relationships have been developed by byssinosis grade, smoking status, and work area (see Figure VI-1). Strong linear associations were consistent findings; regressions for smokers and nonsmokers suggested smokers had a significantly greater prevalence at all dust levels. Similarly, the dose-response relationship between all grades of byssinosis and lint-free dust among those working in slashing and weaving compared with those employed in preparation and yarn processing (spinning, winding, twisting) found consistently lower prevalence rates at all dust levels among the former, presumably because biologically inert sizing contributed to the dust concentration. No threshold effect was evident among the preparation and yarn workers where a dust level of 0.2 mg/m³ was associated with an expected byssinosis prevalence of 12.7% by probit analysis. Among those exposed to slashing and weaving dust, a prevalence of 0.6% was expected at 0.2 mg/m³ exposure and a prevalence exceeding 12.7% was not found until dust levels approached 1 mg/m³.

Fox and colleagues reported correlations between cotton dust (medium and fine fractions less fly) on 1,140 subjects employed in 11 Lancashire mills (69). Again a linear dose-response relationship was observed and found to be im-

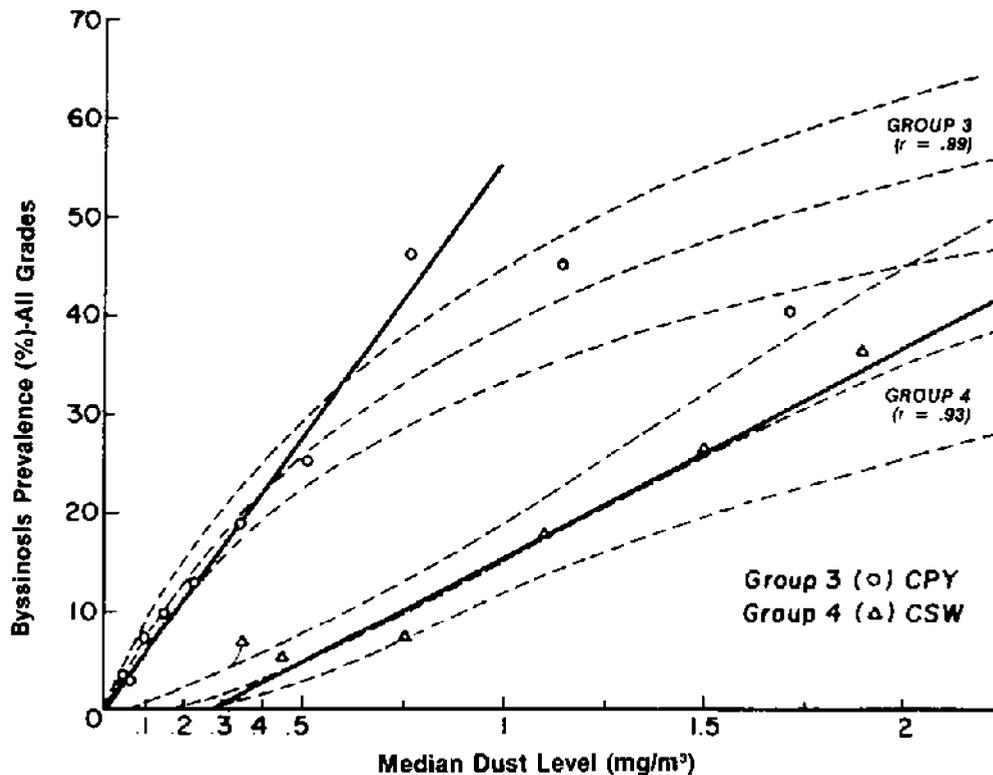


Figure VI-1. Dose-response relationships: Byssinosis prevalence by median dust level among cotton preparation and yard area workers and cotton slashing and weaving workers: linear regressions and fitted probit dose-response curves and their 95% confidence limits. North Carolina, 1970-71.

Source: Merchant, et al. (118)

proved by taking duration of exposure into account. Correlations between bronchitis prevalence and time-weighted dust measurement was not greater among cotton operatives than a separately studied population of control subjects. Regressions for smokers as opposed to non-smokers for byssinosis prevalence and FEV_{1.0} (percent of predicted) suggested that smokers developed abnormalities more rapidly with increasing dust exposure than did those who did not smoke (69).

A number of recent studies have been reported on botanical analysis of cotton trash in various nontextile segments of the cotton industry. These studies have confirmed that cotton bract is the major trash component, but that cotton leaf and noncotton weed material were also major components in most raw cottons (125). Using these analytical techniques, Morey and colleagues have provided an indicator to assess the effectiveness of cleaning processes (124) and to register differences in dust composition in various sectors of the industry such as cottonseed oil mills and the cotton ginning in-

dustry (126). The limited epidemiological data available suggest that dose-response relationships may well be different than those observed in the primary textile industry (86)(169).

Smoking

Evaluation of the contribution of smoking to respiratory disease among textile workers has been hampered by several methodological problems. Among these are failure to account for a possible smoking effect; inadequate numbers to categorize by smoking status and consumption; lack of control populations unexposed to dust; and outward migration from dust and/or tobacco smoke exposure. Therefore, precise evaluation of the relationship between smoking, vegetable dust, and other factors associated with respiratory disease is difficult.

Additionally, there is evidence that selection out of smoking populations also occurs among workers exposed to vegetable dusts. Mair noted the proportion of smokers among flax workers was lower than among controls and suggested that flax work may discourage smoking (102).

This phenomenon has appeared in other studies (22)(35): higher proportions of *former* smokers have been observed in dusty areas (36)(114)(117). Results of two studies suggested that smoking was clearly a more important factor than dust exposure in relation to indices of respiratory disease, but environmental exposure was not well defined, nor was a control population unexposed to vegetable dust considered in either of these studies. Bouhuys and colleagues, utilizing a non-exposed control population and considering retired as well as active hemp workers, concluded that hemp dust exposure was more deleterious, as judged by symptoms of chronic respiratory disease and ventilatory capacity, than was tobacco smoking (23). Similar conclusions have been reached by Bouhuys in his more recent study of a cotton textile community in South Carolina (33).

Merchant et al. studied a large population of cotton workers as well as synthetic and wool exposed controls, and found both cotton dust exposure and smoking to be important factors with cotton dust having a more consistent and significant effect on all pre-shift and shift measures of ventilatory capacity than cigarette smoking (117)(119). Although some smaller studies have not found that smoking contributed to the prevalence of byssinosis (13), studies of larger populations have found byssinosis prevalence to be significantly greater among smokers than nonsmokers (36)(82)(114)(117). When grade of byssinosis was used as an index of severity, statistical analyses have revealed a positive dust exposure and cigarette smoking interaction (111)(114)(117)(119). Smoking is well known to be associated with increased rates of bronchitis, a finding which has also been a feature in most studies of textile workers.

Age and Duration Of Dust Exposure

Factors of age and duration of exposure are considered together since they are usually well correlated in homogeneous populations of textile workers who frequently spend their working years in this trade. Inconsistencies between study populations may be imposed by selection factors such as contraction of the industry, labor competition, wages, and job availability, as well as adverse working conditions. These factors are not detectable in prevalence studies.

No consistent association between age and byssinosis prevalence was found in the study of

Northern Ireland flax workers after accounting for the effects of smoking and duration of flax exposure in sex specific analyses (59). Molyneux and Tombleson, after accounting for duration of cotton dust exposure, mill type and sex, found that byssinosis prevalence increased until age 25 and then remained stable until age 50, after which it slowly declined (123). Other large studies, in which the association between age unadjusted for other factors and byssinosis prevalence has been considered, suggest a weak positive association. Although no evidence of an age association with byssinosis was found in an initial study (114), with a better defined and larger population Merchant found a marginally significant association with age (117). Similarly, the data of Imbus and Suh suggest a higher byssinosis prevalence over age 40 among both smokers and nonsmokers (82). Fox et al. found crude byssinosis prevalence increased with age from 15 to 30 and then stabilized (68).

Although Ferris and colleagues found no association between age and an index of non-specific lung disease among flax workers (65), others have found evidence of an aging effect on persistent cough and phlegm among populations of cotton workers (94)(114). Bouhuys et al. found that hemp workers showed progressively lower FEV_{1.0} levels than nonexposed controls with increasing age (23). Others who have considered measures of expiratory flow by age have observed increased flow rates among those in the highest age categories (82)(157), a finding generally attributed to outward migration of those with low ventilatory capacities in these age categories. There is no evidence to suggest that aging affects the acute decrease in expiratory flow that occurs with dust exposure, or that the rate of annual decline in FEV_{1.0} increases with age category *per se* among workers exposed to vegetable dust (14).

Most studies have found a positive association between duration of vegetable dust exposure and prevalence of byssinosis, although this has not been uniformly observed. Schilling found a progressive increase in byssinosis prevalence over 30 years of dust exposure in his 1955 study of Lancashire cotton operatives (157). Elwood found little evidence of an association with duration of flax exposure among male operatives, but did find a significant association among women independent of smoking and age (59). No evidence of progression from Grade ½ to 2 byssin-

osis was found in this study. Molyneux and Tombleson found byssinosis prevalence increased over the first 24 years of exposure following adjustment for age, mill type, and sex (123). Imbus and Suh (82) and Fox et al. (68) both reporting crude byssinosis prevalence, presented data that suggested an increase in byssinosis prevalence over a 20 to 24 year duration of cotton dust exposure. Bouhuys and colleagues, in a study of a mill with a rapid labor turnover, found that workers exposed to cotton dust for less than a year had a byssinosis prevalence similar to those exposed for longer periods: nearly a quarter of each group had some grade of byssinosis (36). There is some evidence that those relatively new to vegetable dust exposure may have larger shift decrements in FEV_{1.0} (71), and that their annual decline in FEV_{1.0} may be greater than survivors working in vegetable dust for longer periods (14)(116).

Air Pollution

Atmospheric pollution is well known to be associated with increased incidence of chronic cough and phlegm and was thought to be a contributing factor in producing pulmonary disease in Lancashire, where air pollution was significant. Therefore, a study was designed to compare prevalence of respiratory disease in Lancashire and Dutch cotton textile workers exposed to similar concentrations of cotton dust but living in areas where air pollution differed (94). No difference in byssinosis prevalence between the two populations was detected, but the prevalence of chronic cough and phlegm among Lancashire workers was greater than that among Dutch workers. Dutch workers in the town of Almela had more cough and phlegm than workers who lived in the country. These differences could not be accounted for by differences in smoking habit or other characteristics and were attributed to differences in atmospheric pollution. It was also found that Lancashire workers had lower expiratory flow rates, and it was suggested that byssinosis was more disabling when combined with air pollution effects.

Elwood and colleagues considered flax mill locations but found no significant difference in byssinosis prevalence between mills located in urban and rural areas (59). Batawi studied flax workers in an Egyptian town where byssinosis was common yet found little disabling disease (10). He concluded that lack of atmospheric pollution may have been a factor in the low

prevalence of severe disease (10) (153). Bouhuys et al., however, studied Spanish hemp workers in a rural community with negligible air pollution and found disabling pulmonary disease to be common (24)(27). Berry et al., in a study of Lancashire workers between 1963 and 1966, found an "air pollution index" had no relation to annual decline in FEV_{1.0} in this population (14). Air pollution has not been considered a risk factor in American textile mills. The vast majority are located in rural areas of the southeastern United States where air pollution is negligible (111).

Sex, Race, Ethnic Group

Available data suggest no difference in byssinosis prevalence between men and women after other risk factors such as dust level and smoking habit are considered (14)(114)(147). No data is available concerning race in relation to byssinosis prevalence or change in expiratory flow rate with dust exposure. The comparative study of English and Dutch textile workers suggests no difference between these two populations exposed to similar dust levels (94). Similarly, comparison of byssinosis prevalence in large studies of British (68)(123) and American (82)(117) cotton workers suggests that byssinosis prevalence is similar at given dust concentrations in the two populations.

PATHOLOGY

Although a limited amount of anatomic pathological data is available on byssinosis, a good deal of experimental research has been done. This has largely involved clinical pathophysiology, investigations searching for etiological agents, and experimental pathological studies.

Pathophysiology

Clinical observations on the pathophysiology of respiratory dysfunction associated with vegetable dust exposure may be summarized under four headings: pattern of flow rate response, other effects on ventilatory function, radiographic observations, and cellular responses. Studies have utilized small panels of textile workers or volunteers, yet have produced important observations.

Pattern of the Expiratory Flow Response

Previous subject exposure to vegetable dust is not necessary for subsequent significant decre-

ments in expiratory flow rate over a work shift of exposure. McKerrow studied 15 subjects with little or no previous exposure to cotton dust and found 9 developed chest tightness and a marked drop in expiratory flow rate, with a single exposure of 3½ hours (100). Hamilton, who has a childhood history of asthma, studied his own response to cotton dust after minimal previous exposure and observed a dramatic symptomatic and flow rate response (76). (His response, however, was more typical of the immediate response found in asthma in that a significant decrement was observed within 15 minutes and the entire decrement of FEV_{1.0} occurred in 30 to 45 minutes.) The response typical of byssinosis occurs more slowly over two to eight hours of exposure and tends to be linear over this duration (98) (115). The pattern of response varies with the grade of byssinosis both over a day and a week of exposure. Two basic patterns have been described (71). The first pattern is that observed in those with histories typical of Grade 2 byssinosis by Schilling's criteria (157). These workers' expiratory flow decreased each day of exposure, with the greatest reduction on Monday follow-

ing a two-day weekend. These workers tended to recover their Monday morning flow rate between days of exposure. This tendency toward full recovery after a significant Monday decrement has also been observed among workers without chest tightness (71)(113) (Figure VI-2). A second pattern has been observed in workers with intermediate grades of byssinosis and is characterized by a lack of the Monday morning flow rate recovery after a significant Monday decrement. This is typically greater than that of asymptomatic workers but less than that of the Grade 2 byssinotics (35)(42)(71)(113). Despite small numbers of subjects, these observations have been made by several independent investigators and suggested an interesting paradox to Gandevia (70)(71). Why, in a disease thought to progress through grades, would a pattern of physiological response emerge that suggests workers begin with one type of response, then develop the second type of response, and then revert to the first? Epidemiological studies, (14)(59) as well as the observations of McKerrow (99) and Bouhuys (34), suggest the pattern of response does not necessarily progress through grades. McKerrow

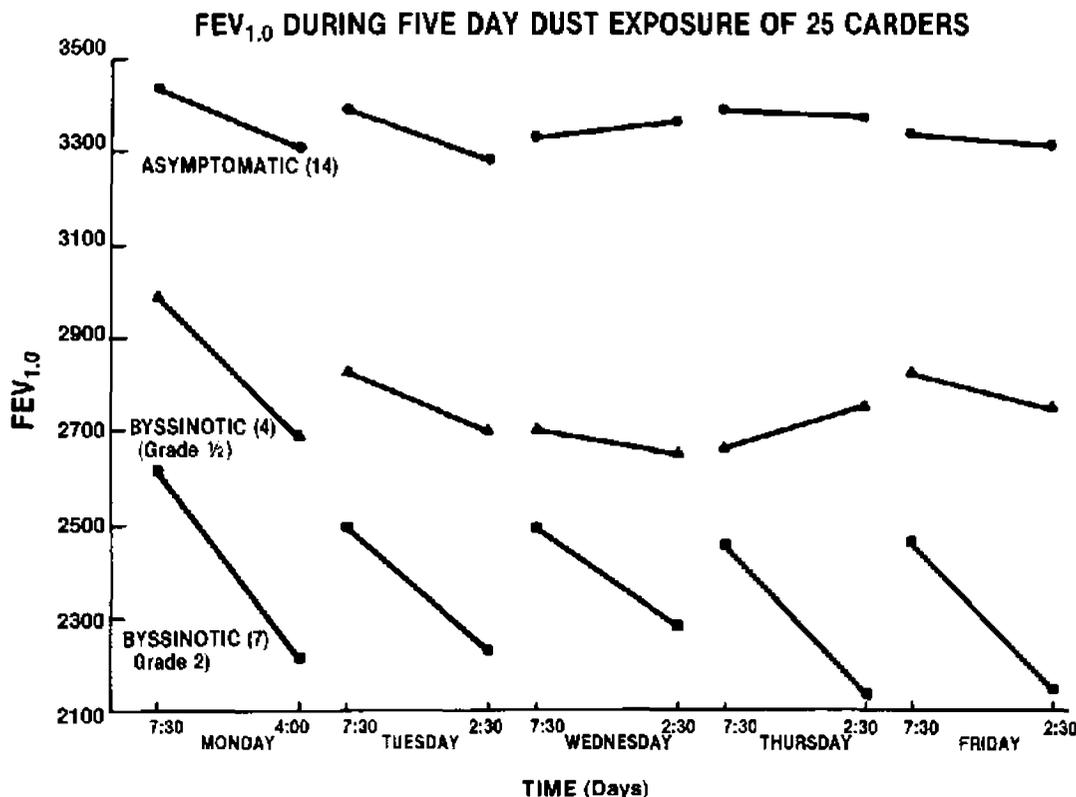


Figure VI-2. Correlation of byssinosis grade and FEV_{1.0} over a workweek.

Source: Merchant, et al. (113)

has further observed that workers with heavier dust exposure tend to have a greater Monday fall in expiratory flow following a two week holiday than after a weekend break, and that byssinotics tend to have a significantly higher FEV_{1.0} after the two week holiday than do nonbyssinotics, who have a significantly lower FEV_{1.0} after the post-holiday Monday exposure compared to other Mondays following a weekend break (99)(100).

Other Parameters of Ventilatory Function

A variety of more sophisticated techniques have been used to study the acute physiological response to vegetable dust. FEV₇₅, frequently reported as indirect maximal breathing capacity (IMBC or MVV) in earlier studies, has been replaced by FEV_{1.0} as the most commonly used test to detect this response. Bouhuys has studied respiratory mechanics with vegetable dust exposure and has advocated the use of flow volume measurements as more sensitive methods of detecting airways narrowing (27)(30)(34)(36). This has been found to be true particularly of partial flow volume curves and maximal flow volume curves at a constant volume (e.g., 60% of the control total lung capacity). Others have also studied a variety of tests in order to determine the most sensitive. McKerrow studied the acute response among rope workers using FEV_{1.0}, FVC, PEF_R, FEF₂₅₋₇₅, FEF₅₀₋₇₅, and FEV_{mid} and concluded that flow measurements provided a slight increase in sensitivity, but that the coefficients of variation for flow measurements were two to three times higher than those for FEV_{1.0} and FVC (97). Merchant and colleagues observed similar differences in variation when comparing FEV_{1.0} and several other parameters including MEFV curves and closing volume (CV) and closing capacity (CC) (112). In this study, FEV_{1.0} provided the most consistent and statistically significant differences over six hours of exposure, largely due to its relatively small variance. CV and CC did not increase significantly, a finding consistent with the view that these tests depend primarily upon elastic properties of the lung which have been found not to change over a few hours of cotton dust exposure (57)(63).

Detailed plethysmographic studies of workers exposed to vegetable dust showed marked increases in FRC and RV and, in some subjects, small but significant increases in TLC together

with decreased FEV_{1.0} and FVC (34)(57)(175). The same authors have reported significant increases in airways resistance. Bouhuys found a decrease in conductance or "conductance response" in the absence of the "flow rate response" (34). Both responses were abolished by bronchodilating drugs, and it was suggested the individual differences may reflect sympathetic innervation patterns of the lung (18). These investigators also found propranolol potentiates the "flow rate response," while atropine inhibits the response. McDermott studied the acute effects of cotton dust, washed cotton dust, coal dust, cigarette smoke, and histamine aerosol on airways resistance as measured by volume plethysmography (96). Airways resistance increased with raw cotton but not with washed cotton. Coal dust concentrations reached 20 times that of cotton dust before resistance increased significantly. Recovery time was delayed following cotton dust exposure while recovery was as rapid as after coal dust following cigarette smoke, histamine, and SO₂.

Evidence that small airways are significantly affected by vegetable dust exposure is supported by studies which have shown nitrogen washout to be reduced (28) and dynamic lung compliance to become more frequency dependent (30)(57). Changes in ventilation/perfusion ratios, with small airways closure, has been the mechanism suggested as the most likely explanation of hypoxemia, which may be marked following a few hours of dust exposure (76)(112)(120). Changes in FEV_{1.0} and increased frequency dependent dynamic compliance were found to last for several days following cotton dust exposure (57). Neither the lung's elastic properties nor diffusing capacity have been found to be affected by acute exposure (57).

Workers exposed to vegetable dust for several years—particularly those with histories of byssinosis—often have pre-exposure ventilatory function indicating airways obstruction, hyperinflation or relative hyperinflation, and hypoxemia (22)(35)(77).

Cellular Responses

Bouhuys first observed that workers exposed to biologically retted flax developed a peripheral leukocytosis over four to six hours of dust exposure and concluded that this may be produced by products of metabolism to bacteria and fungi used in the retting process (35).

Bomsky and co-workers also observed a leukocytic response and a decrease in thrombocytes among some workers exposed to cotton dust (16). Merchant et al. found segmented neutrophils increased significantly in the blood during cotton dust exposure and corresponded temporally with symptoms of chest tightness and decreases in expiratory flow in the panel as a whole, but not in individuals (112). These findings are consistent with leukocytosis observed in experimental animals following tracheal instillation of a cotton dust extract (90)(137). However, the relevance of the leukocyte response in byssinosis *per se* remains to be shown.

Radiographic Observations

Roentgenographic studies of textile workers are notable for their lack of specific findings. Schilling studied 45 age-matched workers, 15 with byssinosis, 15 nonbyssinotic textile workers, and 15 normal controls (156). No significant difference in chest x-ray findings between the groups was observed, except that the byssinotic group had a significantly smaller diaphragmatic excursion. The only other radiographic findings were those found in chronic bronchitis and emphysema. Others have reached similar conclusions in radiographic surveys of cotton workers (58), flax workers (41), and jute workers (102). Although an early American study reported 52 of 88 cotton textile workers to have x-rays suggesting "more fibrosis than usual," pulmonary fibrosis must be considered a rare manifestation of vegetable dust exposure (38). Bolen reported two cases of cotton workers with byssinosis who had radiographic evidence of marked fibrosis together with signs of emphysema (15). Effat reported pulmonary opacities only among workers exposed to cotton with a significant mineral content. The author has seen four workers with long exposures to cotton dust and typical histories of byssinosis, who had fine nodular densities, predominantly in the lower lung zones. All four workers had physiological evidence of airways obstruction with relative hyperinflation. One was found to have sarcoid at open lung biopsy; another was found to have lymphocytic leukemia, which was probably responsible for his opacities.

Apical fibrosis, without evidence of pulmonary tuberculosis, was found in four of 37 workers with long exposure to sisal dust (164). Patchy fibrosis was confined to apical and

posterior segments of the upper lobes and tended to also involve subpleural zones.

Vaskov studied 67 textile workers with obstructive airways disease and/or signs of right-sided heart failure compared to 35 healthy controls (176). Radioisotopes were used to measure circulation times to the pulmonary artery and to the pulmonary vein. Pulmonary function tests showed those with occupational exposure to have evidence of moderate to marked airways obstruction, with a relative increase in residual volume. The venous part of the central pulmonary circulation time was not increased, even among those with right-sided failure, but the earlier part of the circulation time was significantly increased among workers with marked airways obstruction with or without right-sided failure. Pulmonary scintigrams suggested either a generalized or localized loss in pulmonary vasculature, consistent with emphysema, in many of the disabled workers.

Pathogenesis

Critical to experiments dealing with the etiology of byssinosis is agreement on the biological end-point for such studies. Because byssinosis has been defined by a pattern of symptoms, objective criteria such as increased airways resistance or decreased expiratory flow rate have been used to indicate response to cotton dust. A mechanism for chest tightness has been inferred from such findings. However, a hypothesis for respiratory disease arising from vegetable dust exposure must explain Monday chest tightness, associated bronchoconstriction, and ultimately chronic airways obstruction. Although it was once thought that this hypothesis should account for a latent period of several years between first exposure and the onset of typical byssinosis, recent evidence suggest that there may be a short or no latent period at all (23)(36). There is strong evidence, however, that a greater proportion of workers become affected with time (59)(123). Because byssinosis has been defined by acute respiratory symptoms which reflect airways narrowing, attention had been focused on modeling the acute events, with little emphasis on developing experimental models of the chronic process. Although many hypotheses have been advanced, they fall into three mechanisms: a pharmacological mechanism, a microorganism etiology, and an immunological mechanism. All offer an explanation for the Monday phenom-

enon, all overlap in many respects, but not all account for the chronic phase of the disease.

Pharmacologic Mechanism

Similarities between asthma and byssinosis suggested to early investigators that byssinosis may be secondary to histamine and/or histamine-like substances, which were subsequently found in small quantities in vegetable dust (103)(133). It was suggested that dust might release histamine from the lung following accumulation of histamine stores over the weekend (away from dust exposure). With release of histamine, Monday chest tightness would occur but disappear following consumption of the stored histamine (19)(29). To examine this hypothesis, several investigations have assessed histamine release from animal and human chopped lungs *in vitro* and isolated smooth muscle preparations, as well as change in flow rates among affected textile workers or volunteers exposed to various aqueous dust extracts. Using these techniques as assays, extracts have been found to contain contractor substances which are water soluble, dialysable, resistant to boiling, steam volatile, unstable in strong acids and alkali, not destroyed by proteolytic enzymes, and exhibit some pyrogenic activity (77)(80). In addition to small amounts of histamine, serotonin and a kinin-like substance have been identified in cotton dust extracts (3). Paper chromatography of extracts has led some to conclude that polypeptides are the causal agents for histamine release (2). Methyl piperonylate has been identified as one component of cotton bract which is capable of histamine release (80). Although there is now a great deal of evidence that a non-immunological pharmacological mechanism is involved with bronchoconstriction resulting from vegetable dust exposure, it does not necessarily explain the chest tightness which often occurs independent of measurable changes in flow rates, nor does it provide a good explanation of the disease's chronic stage. Therefore, pharmacological events are probably only part of the mechanism of byssinosis.

Immunological Mechanism

The known relationship between skin reactivity and asthma led several early investigators to suggest allergy to some component of cotton dust might be involved in the etiology of byssinosis. Skin testing, often with crude extracts,

has yielded highly variable results which have not contributed to our understanding of byssinosis (45)(139)(140). A classical immunological mechanism unrelated to skin reactivity was proposed by Massoud and Taylor (106)(108). Finding precipitating antibodies to a condensed polyphenol in the serum of textile workers, especially carders and byssinotics, led them to suggest byssinosis might represent an atypical Type III pulmonary disease similar to farmers' lung. Although it was appreciated that granuloma formation, typical of farmers' lung was not a feature of byssinosis, it was suggested this may be attributable to altered "handling" of the inhaled dust (165). Examination of condensed polyphenols by Edwards later showed the precipitin observed by Taylor, et al. was likely explained as a non-specific precipitation of IgG mediated by the polyphenolic polymer (55). Antweiler found little liberation of histamine with the polyphenolic materials (4).

Although the serum precipitins to Taylor's condensed polyphenol may well be nonspecific, double blind trials with byssinotic cardroom workers and nonexposed controls remain to be explained. In these clinical trials, Taylor and colleagues found that aerosol exposure to condensed tannin produced typical Monday chest tightness in those with byssinosis, but not among textile workers without these symptoms, nor in unexposed controls. Although concomitant changes in spirometry were not observed, it is of particular interest that these experimental exposures blocked or markedly diminished byssinosis symptoms upon return to mill work the following day (165).

Microorganism Etiology

Both bacterial and fungal microorganisms have been extensively studied as possible etiological agents. They are found in substantial quantities in textile mill air (45). The occurrence of mill fever and the description of mattress maker's fever, thought to be caused by endotoxins, suggested to early investigators that microorganisms and/or their products may play an important role in byssinosis pathogenesis. Early studies of bacterial and fungal species however, have shown that only rarely are textile workers infected. Attention then turned to endotoxin produced by gram-negative bacteria in mill dust as a possible etiological candidate (137)(14). Among the biological features common to endotoxin and

byssinosis are: tachyphylaxis; pyrogenic properties; leukocytosis; anaphylaxis in lab animals; liberation of histamine; decrease in circulating platelets; fever and tachypnea in rabbits "sensitized" with both cotton dust extract and endotoxin; and cross-reactivity between the two (137) (148). Pernis concluded that byssinosis may therefore be due to the protracted inhalation of small amounts of endotoxin which he interpreted as a condition of "immunological hypersensitivity" (137). Antweiler, however, pointed out that the small amount of endotoxin found in vegetable dust was incapable of releasing histamine; that the smooth muscle constricting substance(s) were stable with boiling; that the endotoxin hypothesis could not explain quantitative differences with different plant parts; and finally, that the clinical picture of byssinosis was not consistent with "hypersensitivity" or an endotoxin effect, fever being conspicuously absent (1).

Nevertheless, recent attention has again focused on endotoxin or enzymes contained in gram-negative organisms as possible etiological agents. Braun, Rylander, and Cinkotai and colleagues have recently shown that the prevalence of byssinosis is roughly correlated with the number of airborne gram-negative bacteria or their products in mill air (37)(46)(149). These relationships have, however, not been as strong as those for nonspecific respirable dust. Because of the stronger association between fine cotton dust and byssinosis prevalence, it is probable that dose-response relationships observed with gram-negative organisms are secondary associations, because these organisms are highly associated with the vegetable dust from which they arise. Although often consistent both epidemiologically and experimentally with certain characteristics of respiratory disease resulting from cotton dust exposure, endotoxin causality has not been established.

Recently, experimental animal studies focused on acute airways changes have been stimulated by the observations of Kilburn who found polymorphonuclear (PMN) cell recruitment to airways surfaces with exposure to raw cotton dust (90). Studies of chemotaxis in Boyden chambers suggest that complement is not necessary for the leukocyte response to occur (William S. Lynn, personal communication). Anecdotal studies of affected workers during dust exposure have shown no change in complement levels.

Studies of complement activation *in vitro*

are of particular interest in regard to PMN recruitment and other pharmacological events. Kutz and colleagues have shown that human complement is consumed by the alternate pathway *in vitro* by both cardroom dust and, to a lesser degree, by treated (washed and extracted) cardroom dust (93). They further showed that nanogram quantities of endotoxin found in cardroom dust could not explain the complement consumption, which would have required microgram quantities of endotoxin. They concluded that other unidentified active substances are involved and speculated that antibody-independent complement activation could explain the accumulation of PMN's in the airways—secondary to complement cascade releasing chemotactic factors, which may induce airway changes via the release of histamine and other pharmacologically active mediators. Similarly, Kilburn noted PMN's are rich in lysosomal enzymes, among which are collagenases and elastases (90); both may play an important role in producing airways narrowing and the chronic airways changes found among severely affected workers.

Experimental Pathology

In earlier studies of experimental pathology, Jotten placed nine rabbits in cages behind carding engines with dust levels from 7.6 to 13.90 mg/m³ (cited by Caminita (40)). Subsequent autopsies revealed diffuse levels of dust and cotton fiber deposits and reactive inflammatory manifestations throughout the rabbit's lungs.

Prausnitz exposed 40 guinea pigs to cotton dust 3 to 4 hours per week for 36 weeks (140). Tachypnea was commonly observed after exposure. Three guinea pigs died of intercurrent pneumonia at 14, 16, and 30 weeks; 3 died but had no pulmonary pathology, and the remainder were sacrificed at 3 to 36 weeks. Those sacrificed after two months had pitted, mottled, and greyish-black pleural surfaces, particularly along the anterior borders of the middle and inferior lobes. The lungs were fixed in inflation and sectioned. Animals that had been dusted for one month had scattered peribronchial nodules, patent alveoli but thickening of alveolar walls with infiltration by polymorphonuclear leukocytes, and edema. Animals dusted for six months showed similar changes with involvement of the entire lung and evidence of a chronic pneumonia. High magnification revealed thickened alveolar walls containing large numbers of polymorphonuclear

leukocytes, large numbers of dust particles in alveolar walls, a small to moderate number of "dust cells," and slight traces of fibrosis. It was concluded that "cotton dust has a great power of penetrating into the deepest parts of the lungs and of producing in them very extensive irritative changes."

Prausnitz also reported histological findings from intradermal injection in his arm of cotton dust protein (prepared by precipitation with ammonium sulfate) (140). After one hour, slight dilatation of capillaries was observed in the papillary region of the dermis with a polymorphonuclear leukocytic infiltration confined to the sweat glands, ducts, and hair follicles. After 16 hours, capillaries were more dilated and there was leukocytic infiltration throughout the dermis and some edema of collagen bundles. There were no plasma cells and only an occasional mast cell. This inflammatory reaction was not observed with intradermal injection of histamine. Prausnitz concluded that the pathology caused by cotton dust inhalation was most likely caused by soluble proteins in dust; that hypersensitivity (based on skin test results) was acquired; and that the pathological changes observed were consistent with chronic bronchitis and emphysema. Alveolar septal thickening was thought to explain dyspnea and to ultimately produce emphysema.

Cavagna and colleagues reported histopathology in rabbits which had inhaled extracts of cotton dust combined with purified *E. coli* endotoxin over a 20 week period (44). All rabbits had bronchitis and bronchiolitis, "bronchial cell exfoliation, endobronchial secretion and parabrachial lymphocyte infiltrates." Alveolar septa were thickened in most animals. Since bronchitis did not appear until after the appearance of endotoxin reacting antibodies, it was concluded it was due to "hypersensitivity" to endotoxin rather than to primary toxicity.

Kilburn et al. studied the effects of cotton dust inhalation (90); condensed complex polyphenols as prepared by Taylor et al. (165); the polyphenolic monomer quercetin; silica flour; barium sulfate; ferric chloride aerosol; and carbon dust. Both guinea pigs and hamsters were exposed and their lungs fixed with intratracheal osmium tetroxide suspended in fluorocarbon. This prevented recruited cells from washing into alveoli from the trachea and from bronchial surfaces. Polymorphonuclear leukocyte recruit-

ment of airways surfaces was observed, particularly with crude extract and Taylor's material within four hours of exposure. It became most prominent at 6 hours of exposure and gradually resolved over 24 hours, at which time there was still an increased polymorphonuclear to epithelial cell ratio. At two hours, polymorphonuclear leukocytes lined the basal lamina of small airways and a few such cells were found between airway epithelial cells. By four hours leukocytes were observed between many airway epithelial cells, beneath the basal lamina, and upon luminal surfaces. Careful study of airway epithelial cells showed no signs of injury such as vacuolation, swelling, crenation, or mitochondrial or nuclear swelling. Alveolar cells and spaces also showed no morphological changes. There was a greater response with one-tenth the concentration of the Taylor material than with the crude extract. Exposure to cotton trash and quercetin dust also resulted in leukocyte recruitment, but not to the degree observed with extracts. Despite massive exposure to carbon dust, there was no evidence of leukocyte recruitment with control dusts.

Rylander has conducted similar aerosol exposure studies in guinea pigs and confirmed Kilburn's observations by counting the number and type of cells lavaged from the lungs following exposure (148). Similarly, Hudson and Halprin have observed marked increases in numbers of leukocytes lavaged from several species of experimental animals after instillation of cotton dust extracts (81). They have also observed a peripheral leukocytosis following an initial relative leukopenia as previously reported by Pernis (137). The time course of these experimentally induced leukocyte responses in animals and leukocytosis observed in exposed human subjects has been consistent with the characteristic delay of one to four hours in onset of symptoms of chest tightness and decreased expiratory flow in textile workers (35)(112).

Anatomic Pathology

Schilling reviewed the pathological observations on lungs of workers with long cotton dust exposure made by several investigators and concluded the pathology was that of nonspecific chronic bronchitis and emphysema (151). The report of Dunn and Sheehan is notable in that good occupational (although not smoking) his-

ories were available, and in that the lungs were fixed in inflation (151). Of the 10 autopsies performed, evidence of pulmonary disease was found in 9, all of whom had worked in dusty areas of cotton mills for over 20 years. All nine showed evidence of chronic bronchitis and/or emphysema which was most marked among the five with histories of stripping and grinding carding machines. These five and two others also had evidence of right ventricular hypertrophy; four of these seven were judged to have died from cor pulmonale. Schilling also described pathological observations made by Gough and Woodcock on lungs of workers with histories of byssinosis (151). Both described emphysema as a prominent lesion. Gough described inflammation of the bronchi with squamous metaplasia and emphysema which was generalized, but somewhat more pronounced in relation to dust deposits. The lungs were further described as having some increase in dust content which appeared to be mainly carbonaceous and only slightly fibrogenic. Gough also described "byssinosis bodies" which consisted of a core of black dust surrounded by a yellowish material which stained positively for iron. These "bodies" were characteristically round or oval and varied in size up to 10 micron. There is at least one pathology case report that suggests pulmonary fibrosis may occur with cotton dust inhalation (144).

The most extensive pathological study of byssinosis has been recently published by Edwards, et al. (56). Lungs from 43 patients who had long exposure to cotton dust, and had been receiving industrial benefits for byssinosis, were distended with formalin at necropsy. Gross examination revealed 27 (63%) with no significant emphysema, 10 (23%) with varying degrees of centrilobular emphysema, and 6 (14%) with panacinar emphysema. Most cases showed heavy black dust pigmentation, often associated with centrilobular dilation of distal air spaces. Microscopic examination showed no evidence of fibrosis, granuloma formation, or vascular abnormality. There was, however, significantly more mucous gland hyperplasia and hypertrophy of smooth muscle in the upper and lower lobar bronchi and significantly less connective tissue and cartilage than in controls. "Byssinosis bodies" were observed in seven cases but thought to be of little significance. Ventricular weights revealed no significant evidence of left or right

ventricular hypertrophy. Although 17 of the 43 were known to be cigarette smokers and all subjects were from the Lancashire area, this study did not assess the possible influence of smoking and/or air pollution.

CLINICAL DESCRIPTION

Clinical Signs, Symptoms and Natural History

The hallmark of byssinosis is the characteristic symptom of chest tightness which typically occurs following a weekend away from work. Although the onset of chest tightness after dust exposure is variable, it is most often observed two to three hours after exposure. This time interval is one important feature distinguishing byssinosis from asthma which usually has an immediate onset with exposure or a later onset (six to eight hours or longer) (17)(20). Affected individuals often compare the feeling of chest tightness to that of a "chest cold". Frequently, chest tightness will be accompanied by a nonproductive cough, especially prominent on Monday. A history of chronic, often productive cough is frequently obtained. In older workers who have been exposed to cotton dust for many years, a history of exertional dyspnea is a common finding. Among those severely affected, chest tightness and dyspnea occur on all work days with relief only on weekends and holidays, if then.

All symptoms become more severe if the period away from cotton dust exposure is prolonged; i.e., the affected individual appears to lose exposure tolerance. Conversely, Monday symptoms do not occur if exposure occurs seven days per week. Symptoms are often more severe and more frequent among smokers. Occasionally a worker will report that his symptoms of Monday chest tightness disappeared when he stopped smoking, even though his dust exposure did not change.

There are no typical or characteristic signs to be found upon physical examination of byssinotic subjects who are not severely affected. While the subject will frequently exhibit a productive cough, on auscultation of the chest it is usually relatively quiet except for occasional rhonchi. Wheezing is not commonly found early in the course of the disease. Among those severely affected, all of the physical findings of advanced chronic bronchitis or emphysema may be observed.

A number of nonspecific symptoms are experienced by those exposed to cotton dust, with or without byssinosis. Cotton dust is an irritating material which dries and inflames mucous membranes resulting in mild conjunctival irritation, sneezing, and hoarseness. Chronic cough and phlegm and exertional dyspnea are also observed among cotton workers who have not smoked and recall no typical history of byssinosis. Whether these individuals merely forgot they once had symptoms on Monday or developed these nonspecific symptoms without the typical periodicity is not well understood. Available data suggest the latter.

New workers and those who first go into dusty cotton processing areas for a period of a few hours may experience "mill fever" (5) which has been also called "weaver's fever, cardroom fever, dust chills, dust fever, cotton cold, cotton fever," and among flax workers "heckling fever" (35). Symptoms, which occur within 12 hours of exposure, consist of chills, headache, thirst, malaise, sweating, nausea, and vomiting accompanied by a transient fever. Without further exposure these symptoms subside spontaneously within a day or two. With repeated exposure, such as that experienced by a new worker, these symptoms may occur for several days until the worker is "seasoned" (5) or develops tolerance. Another common complaint of new workers or visitors to mills is tobacco intolerance following exposure to higher concentrations of cotton dust. These symptoms are not often observed at lower dust exposures and are, therefore, becoming less common as dust control improves within the cotton processing industries.

A second group of febrile syndromes associated with cotton processing includes "Mattress-Makers' Fever" and "Weavers' Cough". These conditions occur among experienced workers and are characterized by a high attack rate, a clear-cut febrile episode, severe cough, and dyspnea. Most of these epidemics have been attributed to mildweed yarn. An endotoxin containing gram-negative bacillus, *Aerobacter cloacae*, has been isolated and was thought to be the likely etiological agent in one of these outbreaks (129).

Clinical Laboratory Investigations

Clinical laboratory evaluation of workers affected by textile vegetable dust usually does not

occur until function has become impaired. At that point, a thorough pulmonary evaluation, including chest x-ray and spirometry, are indicated. Although the chest radiograph can produce no specific information to associate impairment with occupational exposure, it is important to eliminate other pulmonary pathology such as tuberculosis, lung cancer, and pulmonary fibrosis. If a worker is significantly impaired, this will usually be clear from spirometry assessment. In cases where symptomatology and functional changes do not coincide, a fuller assessment of lung function, including diffusing capacity and lung volumes, may be useful. The most direct route to determining impairment is assessment of arterial blood gases at rest and, if necessary, with exercise. This invasive procedure is not indicated except in borderline cases where the level of impairment or other abnormality is not clear (see section on "Criteria for Assessing Impairment").

Treatment

Research on byssinosis therapy has been confined to acute events. Clinical trials have relied almost exclusively on changes in flow rates among active workers as indicators of effect. While propranolol has been shown to increase bronchoconstriction with hemp dust exposure, antihistamines and ascorbic acid have been found to protect against this effect (172)(174). Similarly, it has been found that inhaled bronchodilators (salbutamol, isoprenaline, and orciprenaline) will prevent or reverse flow rate changes (64)(87)(173)(181). Finally, it has been found that pre-exposure treatment with disodium chromoclycate tends to block bronchoconstriction (64)(178). Inhaled beclamethazone also appears to decrease the flow rate response (64). It must be emphasized that the beneficial effects observed were functional, without similar documentation in regard to symptomatology. Although the bronchoconstriction effects of these dusts (which is usually not severe) may be blocked or reversed, there is no evidence that use of these drugs will necessarily suppress byssinosis symptoms or retard the progression of cotton dust-induced obstructive airways disease: they cannot be considered preventive measures. Among those who are severely affected, therapy is that for chronic bronchitis and emphysema (see section on "Chronic Airways Obstructive").

Prognosis

The prognosis of the worker affected by textile vegetable dusts is highly dependent upon the stage at which the effect is identified and upon subsequent exposures. Workers often select themselves out of dusty areas which they perceive to affect their respiration. This is particularly true of asthmatics and others with "twitchy airways" who will often transfer out of dusty areas within days or weeks of first exposure. As a result, the likelihood they will develop chronic impairment is slight. Similarly, those without symptoms but with functional changes observed over a work shift may be identified through medical surveillance. If their baseline function is normal and they transfer out of dust exposure, their prognosis should be excellent. If they continue to be exposed, available evidence suggests that their lung function may be expected to decline at an accelerated rate (14)(116). This is particularly true for those who are exposed at higher dust concentrations and for those who smoke (67) (116). Smokers who stop smoking have been found to revert to a normal rate of annual decline in function, but will not recover the function loss already sustained (67).

Whether this is also the case among those affected by vegetable dusts is not known. It is known that lung function will continue to improve over a period of at least ten days away from dust exposure, but that function is largely recovered following only a weekend away (111). These observations have been made among active workers with reasonably normal baseline lung function. It is probable workers with significant airways obstruction may recover some functional loss over a longer period of time. In the one study which assessed former flax workers, a number of interesting observations were made (unfortunately, lung function measurements were not available): Older men, with a history of byssinosis or high flax dust exposure, were more likely to give exertional dyspnea as the reason for leaving the mill. Several with symptoms of byssinosis stated their symptoms improved after leaving exposure, but two with severe byssinosis reported they continued to become progressively worse (59). These observations are consistent with the clinical experience of the author.

As has been observed in other studies of chronic airways obstruction, prognosis is closely tied to level of impairment as measured by spirometry. When this level of impairment is marked

and cannot be improved by avoiding dust and cigarette smoking exposure or by bronchodilation or steroids, spirometry has proven to be the best single prognostic sign (39)(85)(146)(167). There is no reason to believe this is not also true for chronic airways obstruction produced by the textile vegetable dusts.

DIAGNOSTIC CRITERIA

The criteria used in assessing the health effects of textile vegetable dusts are dictated by their application. For epidemiological studies, Schilling's criteria (see page 536) has proven to be reliable and valid. These criteria are, however, entirely subjective, making them less useful for surveillance programs which may involve a recommendation to retire or transfer a worker to another job. Criteria based on functional changes have been introduced (see Table VI-4). These criteria offer the advantages of objectivity and replication, which is important because of inherent variability in individual spirometric measurements. Using this scheme, corporation-wide surveillance programs may be carried out which may both describe the prevalence of functional changes and provide a mechanism for management of currently employed workers (105).

Neither of these classifications (which have been used extensively among currently employed workers) are by themselves suitable for disability evaluation. Schilling's classification is subjective and defines only part of the biological effect. Bouhuy's functional classification is dependent upon in-mill exposures and measurements, and defines only part of the biological effect. Both classifications, however, provide useful information to physicians assessing impairment and disability.

Probably no area in chest medicine suffers as much confusion as does the terminology of chronic obstructive diseases (66). Included in this group are chronic bronchitis, emphysema, asthma, and byssinosis. Physicians frequently disagree in diagnosing these diseases which are multifactorial in etiology and overlap functionally, pathologically, and by available definitions (66). A good deal of effort has been given to deriving acceptable definitions for these entities. Except for emphysema, which has been defined pathologically but not well clinically, we still have no uniform, acceptable international definitions. Because of the Schilling and Bouhuys classifications, there are probably more uniformly applied definitions for byssinosis than these other en-

tities. Yet, they do not provide adequate diagnostic criteria to assess impairment and disability among textile workers. At the same time it has been estimated there are several thousand textile workers who are severely impaired, at least in part because of their exposure to cotton dust (33).

To deal with this, based upon epidemiological data, allocation of risk may be applied to individuals for whom risk factors have been measured. No physician can measure the effect of cotton dust, cigarette smoke, infection, ambient air pollution, or genetic constitution in an individual. With detailed knowledge of these factors he may be able to draw a reasonable opinion, but it is doubtful that another physician with the same information would come to the same conclusion.

Among those exposed to the textile vegetable dusts, there are two overwhelming risk factors associated with respiratory symptoms and impaired function—dust exposure and cigarette smoking. Large cross-sectional studies, as well as some prospective studies, have shown both to be important. Further, it is known that although those with byssinosis symptoms and acute functional changes may progress more rapidly, others also progress at accelerated rates, depending on dose of dust and smoking. Therefore, all individuals with a significant dust exposure could justifiably be allocated at increased risk and presumed to have acquired at least some of their impairment from their occupational exposure.

The first important determination is to define "significant exposure" in order to distinguish those eligible for such allocation. The British require five years employment in an area of cotton textile preparation and yarn exposure (121). Based on cross-sectional and prospective data, it is unlikely that significant irreversible impairment would occur over a shorter period. There is American data which would support inclusion of cotton textile workers in the areas of preparation, yarn processing and weaving.

The second important determination is objective assessment of airways obstruction (see "Criteria for Assessing Impairment"). Spirometry will usually provide an excellent indication of impairment. If necessary, arterial blood gases at rest or with exercise will better define cases with borderline spirometry. Medical history, physical examination, and other laboratory tests

should provide a clinical picture compatible with chronic obstructive lung disease and also serve to eliminate other medical conditions or diseases such as tuberculosis, lung cancer, hypersensitivity pneumonitis, etc. These entities do not arise from employment in cotton mills but may result in pulmonary impairment.

PREVENTION

Given our current state of knowledge about the etiology of byssinosis and lack of an environmental biological assay, risk assessment is dependent upon assessment of dust concentrations (31). Similarly, prevention is dependent largely upon dust control in the workplace. Significant improvements in exhaust ventilation control technology and application have recently resulted in reduced risk in many areas of textile mills in the United States. A second control technology, which appears promising experimentally, is washing cotton (9)(115). Although this procedure has been found to reduce symptoms and functional changes, largely through removal of fine dust, it is not yet clear whether cotton washing is technically feasible on a large scale. Cotton steaming studies have shown equivocal results (83)(116).

While dust control is the foundation of a respiratory disease prevention program in the cotton processing industries, medical surveillance and employee education also play important roles. Smoking and the interaction between smoking and cotton dust exposure are clearly important risk factors in respiratory disease among textile workers. Therefore, it is essential that information about the adverse effects of smoking, particularly in combination with cotton dust exposure, be provided to those exposed. Similarly, it is essential that work practices which affect individual dust exposure be stressed. Periodic medical examinations designed to detect those acutely affected and those with chronic lung disease are important and can be effective. Through the use of a standard questionnaire, it is possible to ascertain a sound occupational and smoking history, and screen for byssinosis, bronchitis, dyspnea, and other medical complaints. Simple spirometry, routinely applied, will identify many of those acutely affected and nearly all with significant impairment.

All of these prevention provisions—allowable dust concentrations, work practices, and medical surveillance—are detailed in the Depart-

ment of Labor Cotton Dust Standard promulgated in 1978 (170). Compliance with the provisions of that standard would largely eliminate byssinosis and prevent significant occupationally related pulmonary impairment among United States cotton textile workers.

RESEARCH NEEDS

Research is needed to fill gaps in vegetable dust exposure epidemiology, lung injury mechanisms, and control technology. Other organic dusts, such as grain dust, pose problems similar to the textile vegetable dusts; therefore, appropriate research will have far-reaching consequences.

Epidemiological Research

1. Cross-sectional studies of the nontextile cotton industries to establish dose-response relationships.
2. Prospective and community studies to account for outward migration, and to better quantitate risk factors and their interactions on prognosis.
3. Studies targeted at former workers to better establish their impairment and reversibility levels after leaving employment.
4. Dose-response studies of flax dust exposure.

Mechanism Research

1. Development of a reliable animal model of chronic airways effects to facilitate research on etiological agents and to more fully assess toxicological properties of dust from various sectors of the cotton industry.
2. *In vivo* and *in vitro* studies of mediators, complement and their interactions as related to lung injury arising from exposure to textile vegetable dusts.
3. *In vivo* and *in vitro* studies targeted at the interaction of vegetable dusts and cigarette smoke to interpret the mechanisms by which smoking increases susceptibility.
4. To relate *in vitro* and *in vivo* studies to clinical byssinosis, controlled trials involving human subjects are essential.

Control Technology Research

1. Textile machinery research to develop desirable alternatives to processes such as

spinning frames (i.e., open end spinning) to achieve more efficient processing together with good dust control.

2. Research into the feasibility and effectiveness of cotton washing or other treatment to eliminate respirable dust and/or "detoxify" dust which may remain. Prospective epidemiological studies would establish the medical effectiveness of such a process.
3. Development of closed-boll growing, harvesting, and processing of cotton to preclude contamination of the cotton fiber with cotton trash.
4. Development of basic ventilation exhaust systems for certain nontextile cotton processes found to be associated with hazardous dust levels.

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SECTION VII
EFFECTS OF INHALED TOXIC AGENTS

ACUTE AND CHRONIC RESPIRATORY EFFECTS OF EXPOSURE TO INHALED TOXIC AGENTS

Robert Frank

INTRODUCTION

This chapter covers the acute and chronic effects of exposure to inhaled toxic agents. The chemical agents discussed are hazardous primarily to the respiratory system. Some also affect distant organs or tissues. Examples of the latter are mercury and cadmium, which are toxic to kidneys. How extensively the respiratory system is involved, particularly following acute or accidental exposure, is determined largely by the concentration of the agent and duration of exposure. Other factors that may modify the individual's response include pre-existing heart or lung disease, prior long-term exposure to the same agent, level of activity during exposure, and age.

The symptoms and signs of mild exposure to irritant gases that are relatively soluble in aqueous solution (e.g., ammonia, chlorine, and sulfur dioxide) are likely to be confined to the upper airways within the head. In response a subject may experience one or more of the following: sneezing, nasal catarrh, unpleasant smell or taste, soreness of the throat, smarting of the eyes and lacrimation.

More intensive exposure extends the involvement to the central airways of the tracheo-bronchial tree. Cough, sputum, pain, or constriction of the chest—and in the event of bronchospasm—shortness of breath, and wheezing, may be prominent. If there is excessive production or retention of mucus, or if portions of the lining of the airways slough away, rhonchi may be heard. Spasm of the larynx may totally obstruct the airway requiring an immediate tracheotomy.

The most intense exposures damage the alveolar-capillary membrane or parenchyma of the lung. The consequence is edema. Depending on the amount of edema that forms, a subject may suffer extreme shortness of breath, dusky discoloration of the mucous membranes and nail

beds (cyanosis), blood-tinged sputum mixed with foam, and collapse. Rales are heard overlying the edema. Sometimes initial evidence of edema is only vague and premonitory; consequently, the patient or examiner may underestimate the gravity of the condition.

The physiologic changes that occur are not unique to the chemical agent itself, but reflect the portion(s) of the respiratory system involved and the intensity of that involvement. If the laryngo-tracheo-bronchial tree is constricted, maximal ventilatory flow rates fall. Techniques are now available for making the important distinction between involvement of larger central airways and smaller peripheral airways. If constriction is peripheral, there is associated air-trapping. If, as usually happens, constriction is irregular in pattern, another group of tests can be used to show that the distribution of ventilation within the lung is uneven and abnormal, and that gas-exchange across the alveolar-capillary membrane is impaired. Impairment of gas-exchange leads to hypoxemia or retention of carbon dioxide (hypercapnea).

Chest pain and weakness from any cause tend to limit a subject's ability to inspire maximally. Consequently, any measurement that depends on a maximal inspiration—including the commonly used forced expiratory vital capacity (FVC) and 1-second forced expired volume ($FEV_{1.0}$)—will be affected apart from any changes imposed by narrow airways or stiffened lung parenchyma.

Edema reduces the subdivisions of lung volume, including total lung capacity (TLC) and vital capacity (VC). Edema also stiffens or reduces lung compliance and interferes with oxygen diffusion into the blood. Hypoxemia commonly follows edema. Chest x-rays are a useful means of assessing the amount and extent of edema.

Pollutant gases with relatively low solubility

in aqueous solution tend to shift their primary effect to the periphery of the respiratory system. Thus, ozone and nitrogen dioxide, in contrast to sulfur dioxide, are notable for the bronchiolar and parenchymal injury they produce at relatively low concentrations (1)(2). Sulfur dioxide, being more soluble, is likely to affect the upper airways and large central airways.

The effect of an irritant or toxic agent contained in an inhaled particle is intimately related to the aerodynamic behavior of the particle, since aerodynamic behavior is a determinant of where and how much deposition occurs within the respiratory system. Cadmium, vanadium, and sulfuric acid are examples of noxious agents that are inhaled in particulate form. A useful, concise review of the routes of entry and modes of action of gases, vapors, and particles was published by Stokinger (3).

The respiratory system has several means of clearing itself of infectious or inanimate particles. Most solid particles that deposit in the alveolar region are engulfed by macrophages, which are mobile cells that transfer the material to nearby terminal airways. A small, variable fraction of these particles may pierce the alveolar lining and either imbed in fixed tissues or be removed through lymphatics or blood vessels. The mucociliary system, beginning with the terminal bronchioles, carries particles from the nasal passages and from the lower airways toward the throat; the particles are then swallowed or expectorated. Cough is effective in clearing the central airways. The dosage to the lung of chemicals contained in solid particles is a complex function of ambient concentration, deposition rate, and clearance efficiency. The chemical agents discussed in this chapter all have the potential for impeding clearance and thereby influencing dosage.

Functional impairment is not synonymous with disability. For example, a specified reduction in ventilatory performance may not affect a sedentary worker, whereas it could disable a professional athlete. Disability may have a component that is hard to objectify. If there is uncertainty or dispute over disability and functional testing is to carry weight in the decision, it is preferable to rely as much as possible on tests that do not depend on voluntary performance.

It may be relatively simple to identify and describe the clinical and laboratory features of massive overexposure to a specific agent, but

to detect the onset of subtle changes associated with prolonged low-level exposure and identify the cause with reasonable certainty is often difficult because laboratory findings upon which the diagnosis may rest are not always sharply divided between "normal" and "abnormal"; and because values may fluctuate within a healthy individual and differ widely among the population. To detect small deviations from normality, therefore, requires standards based on a control group that is similar to the workers at risk in terms of age, sex, race, and socioeconomic status. Detection of early abnormality improves with periodic testing, the latter being typical of so-called prospective studies, but this approach is not often used because of its expense and inconvenience. Once illness is established and the worker is removed from the offending environment, periodic testing becomes vital to determine the rate and extent of recovery or reversibility.

Above all, the detection of early or slowly progressive illness in a worker, along with identification of the cause, requires a careful, probing history. Information should be obtained about competing risks such as cigarette smoking and about variables such as socioeconomic status or nutritional habits that may alter the response to a specific hazard. Nonoccupational environments, including the home, may also contribute to specific airborne exposures, as with nitrogen oxides and carbon monoxide. Food, drink, and absorption through the skin may add to the total body burden of heavy metals. The current state of the art renders it difficult to predict the potential severity of future impairment from acute exposures and this difficulty is compounded by the usual lack of information about dosage in acute exposures. Such information gaps make case comparisons difficult. Consideration of how these independent variables may interact with an identified occupational risk can be vital to the clinical or epidemiological assessment.

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AMMONIA

Introduction

Among the gases considered in this chapter, the most soluble in water is ammonia (89.9 g/100 ml at 0°C). In solution, a strong alkali, ammonium hydroxide (aqua ammonia) is formed. The high solubility and strong alkalinity make ammonia especially irritating to the upper airways. The gas, which is colorless, has an easily recognized odor. It liquefies at -33.3°C.

Ammonia is used as a source of nitrogen in fertilizers (agriculture is a relatively frequent setting for accidental overexposure), as a commercial refrigerant, and in a wide variety of industrial and commercial activities. Table VII-1 of the NIOSH criteria document for ammonia lists 82 occupations that are implicated (9). It is estimated that over 3,000,000 workers are potentially at risk to the hazards of ammonia (8).

The current federal standard for ammonia is 50 ppm (35.7 mg/m³) based on an 8-hour time-weighted-average (TWA). It has been recommended that the same numerical standard be expressed instead as a ceiling based on a 5 minute sampling period (9).

Acute Exposure, Human

Ammonia is unusual in that it is produced in the body (particularly in the oral cavity) and released continuously into respired air. The concentration of ammonia in air exhaled by mouth is on the order of 0.2 ppm (6). The hypothesis has been made that this endogenous ammonia may neutralize—and thereby mitigate—the effects of inhaled acid aerosols such as sulfuric acid (6).

The threshold for detection of ammonia by smell varies as reported by different investigators (9). Most of these reports provide inadequate information about test methods. Fifty ppm is known to impart a strong smell (10). Brief exposure to 100 ppm increases nasal air flow resistance, thought to be attributable to vascular

congestion, edema, and increased mucus secretions (7). This effect is perceived as “stiffness.”

There are two sources for our knowledge of the respiratory effects of acute exposure to ammonia: controlled laboratory studies and accidents. In laboratory experiments, mild irritation of the eyes, nose, and throat is provoked by 50 ppm but not by 25 ppm (5)(13). Among the subjects tested, “experts” familiar with the reported effects of ammonia and of the opinion that “it will do little or no harm” have expressed fewer complaints than have “nonexperts” (13). Nonexperts could not tolerate exposure to 140 ppm for 2 hours, chiefly because of an urge to cough. Neither group showed any impairment of function as measured by VC and FEV_{1.0}. Acclimation to 50 ppm developed within one week (5). One hundred ppm became easily tolerated within 2 to 3 weeks of repeated exposure.

In an earlier laboratory study, volunteers were exposed to 500 ppm of ammonia for 30 minutes by oro-nasal mask (11). Aside from the expected irritation of the skin beneath the mask and of the upper airways, the most significant physiologic response was hyperventilation and an associated increase in respiratory rate. (By contrast, sensory irritants typically reduce respiratory rate in rodents; see also Chlorine (1).) There was no coughing, however, exposure to 1,000 ppm of ammonia caused immediate coughing.

Together, these studies offer little evidence of physiological abnormalities in the lower airways among healthy subjects either in response to 500 ppm for 30 minutes or to lower concentrations for intervals lasting up to several weeks.

Massive accidental exposure to ammonia can be rapidly fatal. Concentrations in the range of 700 ppm to 1,700 ppm can be incapacitating due to extreme lacrimation and coughing (5). The eyes, skin, and all levels of the respiratory tract may be severely inflamed. The clinical and physiologic abnormalities associated with acute, extensive injury to the respiratory tract have been outlined in the Introduction to the chapter.

The pathologic changes that may develop are described in the report of a fatality occurring 60 days following exposure to anhydrous ammonia (12). The report provides a tabulation of autopsy findings of other authors. Severe damage at every possible level within the respiratory system is mentioned, ranging from purulent oro-pharyngitis to edema, hemorrhage, and

Table VII-1
OCCUPATIONS WITH POTENTIAL EXPOSURE TO AMMONIA

Acetylene workers	Manure handlers
Aluminum workers	Metal extractors
Amine workers	Metal powder processors
Ammonia workers	Mirror silverers
Ammonium salt makers	Nitric acid makers
Aniline makers	Organic chemical synthesizers
Annealers	Paper makers
Boneblack makers	Perfume makers
Braziers	Pesticide makers
Bronzers	Petroleum refinery workers
Calcium carbide makers	Photoengravers
Case hardeners	Photographic film makers
Chemical laboratory workers	Plastic cement mixers
Chemical manufacturers	Pulp makers
Coal tar workers	Rayon makers
Coke makers	Refrigeration workers
Color makers	Resin makers
Compressed gas workers	Rocket fuel makers
Corn growers	Rubber cement mixers
Cyanide makers	Rubber workers
Decorators	Salt extractors, coke oven by-products
Diazo reproducing machine operators	Sewer workers
Drug makers	Shellac makers
Dry cleaners	Shoe finishers
Dye intermediate makers	Soda ash makers
Dye makers	Solvay process workers
Electroplaters	Stablemen
Electrotypers	Steel makers
Explosive makers	Sugar refiners
Farmers	Sulfuric acid workers
Fertilizer workers	Synthetic fiber makers
Galvanizers	Tanners
Gas purifiers	Tannery workers
Gas workers, illuminating	Textile (cotton) finishers
Glass cleaners	Transportation workers
Glue makers	Urea makers
Ice cream makers	Varnish makers
Ice makers	Vulcanizers
Ink makers	Water base paint workers
Lacquer makers	Water treaters
Latex workers	Wool scourers
Maintenance workers (janitors)	

Adapted from NIOSH.

consolidation of the parenchyma.

Chronic Exposure, Human

No epidemiological studies adequately designed to test the (possible) harmful respiratory effects of chronic, low-grade occupational exposure to ammonia have been reported. This is surprising in view of the large, diverse population of workers potentially at risk. Available reports have been judged inadequate (9). One personal communication from an official of the Division of Occupational Hygiene in Massachusetts refers to the odor and slight sensory irritation associated with levels of ammonia at or below 45 ppm in proximity to refrigeration equipment; there is no mention of any clinical or physiologic assessment.

As noted under Acute Effects, informal evidence suggests that acclimation of the upper airways to the sensory irritation of ammonia, and particularly of the sense of smell, is common.

Animal Effects

There have been several histologic studies of the lungs and other tissues following repeated exposure of animals to ammonia. None were combined with physiologic measurement.

Coon et al., in a screening procedure, exposed rats continuously to about 365 ppm of ammonia for 90 days (3). About one-fourth of the animals developed mild nasal discharge; a smaller fraction had slight increases in blood leucocytes suggestive of an infection; and the lungs and kidneys of the entire group showed "nonspecific circulatory and degenerative changes." Lower concentrations of ammonia (220 ppm or less) over the same or slightly longer period of time had no histologic or hematologic effects. Concentrations of about 635-640 ppm caused eye and nasal irritation, labored breathing and death in a majority of the animals within 65 days, when the experiment was terminated. (Among the other species exposed to these concentrations, about one-fourth of the guinea pigs died and no deaths were reported among rabbits or dogs.) In another study involving exposure of guinea pigs to about 170 ppm for up to 12 weeks, evidence was found of structural changes in a number of abdominal organs but not in the lungs (14).

There is evidence that ciliary beat rate, and by implication mucociliary clearance, is depressed in an excised rabbit tracheal preparation directly exposed to ammonia for several minutes, beginning at about 100 ppm (4); that bacterial

clearance from the lungs may be impaired after 2 hours of exposure to an estimated 50 ppm of ammonia; and that the prevalence of infectious disease in rat lungs caused by *Mycoplasma pulmonis* is related to the concentration of ammonia in the range of 25 ppm to 250 ppm, when the gas is administered over a 4 to 6 week period (2).

Recommendations

Further studies on the possible effects of ammonia on lung clearance are warranted in animals and, if possible, in human subjects. These studies should include concentrations of the gas at or near the present standard of 50 ppm.

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CADMIUM

Introduction

Several forms of cadmium are hazardous to workers, including the elemental metal, oxide, chloride, and sulfate salts. All occur as respirable dusts, and the metal also vaporizes if heated. At the melting point of cadmium (321 °C), the concentration of the vapor may exceed 560 mg/m³ (3). On an equal weight-basis, the vapor is considered more toxic than the dust.

Cadmium is usually recovered as a by-product in the processing of zinc, copper, and lead ores. Most of the approximately 5,000 tons of cadmium used annually in the United States are for electroplating and production of alloys. It is estimated that nearly 2,000,000 workers are potentially at risk to cadmium (18). A partial list of these occupations is shown in Table VII-2, revealing the rich variety of uses made of the metal (22).

The federal standard for cadmium fume is 0.1 mg/m³ based on an eight-hour time-weighted-average (TWA); the ceiling concentration is 0.3 mg/m³. There is a separate eight-hour standard for the dust of 0.2 mg cadmium/m³, together with a ceiling concentration of 0.6 mg/m³.

NIOSH has recommended that the stan-

dards for fumes and dusts be consolidated into a single total particulate standard of 40 µg/m³ (TWA), and that the ceiling be lowered to 200 µg/m³ (0.2 mg/m³) based on a 15-minute sampling period (19). The rationale underlying the first recommendation is that fumes represent small particles without a precise definition of size, form a continuum with larger dust particles, and all may be sampled together. Because cadmium is volatile at high temperature, workers in heated environments may be exposed to hazardous concentrations of the vapor that could pass undetected by the popular sampling method which relies on cellulose ester membrane filters.

Acute Effects

Several possible mechanisms for the toxicity of cadmium have been proposed. One is that cadmium inhibits a number of oxidative enzymes, perhaps by displacing essential metals such as zinc from their structure (9). Second, that cadmium promotes the formation of metallothionein, a protein said to contribute to toxicity. The precise effect of metallothionein on normal protein synthesis is unknown. Third, based on *in vitro* evidence, that cadmium depresses the alpha-1-antitrypsin level of blood (4)—alpha-1-antitrypsin acts as a curb on trypsin, a lysin thought to play a role in the development of emphysema. This observation has not been confirmed (26).

Most cases of acute intoxication have been associated with welding, brazing, or soldering (22). The manifestations of toxicity are chiefly respiratory. The onset of symptoms may be delayed several hours, or until the worker has left the scene of exposure. The severity of exposure determines the extent of respiratory involvement, and consequently, the symptoms, signs, and prognosis. Slight exposure is attended by drying and irritation of the upper airways, sneezing, and a metallic taste. Cough and chest pain signal involvement of the lower airways. Involvement of the parenchyma leads to edema. Shortness of breath and cyanosis are then likely to dominate the clinical picture. Pulmonary edema may occur within hours of severe exposure and persist for days or weeks.

Symptoms of systemic intoxication, i.e., headache, nausea, vomiting, chills, muscular aches, diarrhea, and weakness, may follow shortly upon the onset of respiratory complaints. The clinical picture may simulate that of an acute infection, or be mistaken for metal fume fever,

Table VII-2
OCCUPATIONS WITH POTENTIAL EXPOSURE TO CADMIUM

Alloy makers	Incandescent lamp makers
Aluminum solder makers	Jewelers
Auto mechanics	Lithographers
Battery makers, storage	Lithopone makers
Bearing makers	Metalizers
Braziers and solderers	Paint makers
Cable and trolley wire makers	Paint sprayers
Cadmium-compound collecting-bag handlers	Pesticide makers
Cadmium platers	Pharmaceutical workers
Cadmium smelters	Photoelectric cell makers
Cadmium vapor lamp makers	Pigment makers
Cadmium workers	Plastic products makers
Ceramics, pottery makers	Sculptors, metal
Copper-Cadmium alloy makers	Small arms ammunition makers
Dental amalgam makers	Smoke bomb makers
Electric instrument makers	Solder makers
Electrical condenser makers	Textile printers
Electroplaters	Welders, cadmium alloy
Engravers	Welders, cadmium-plated objects
Glass makers	Zinc mining, smelting and refining workers*
Hobbyists, metal	

*Mineralogically, cadmium and zinc occur together.

Adapted from Blejer (1971, Appendix A, II)

particularly among welders. Systemic intoxication may be accompanied by proteinuria, perhaps a reflection of injury to renal tubules.

The mortality rate in the presence of pulmonary edema may reach 15-20%. The lethal dose of cadmium is estimated to be about 2,500 mg-min/m³ (19), and fatalities have been reported following exposure to 40-50 µg/m³ for one hour (23). While recovery from edema generally appears to be complete within weeks, shortness of breath and impaired pulmonary function persist for years in some instances.

Chronic Effects

Exposure to cadmium is not limited to occupational setting. Cadmium contaminates ambient air, drinking water, food, and cigarettes. Generally, the concentrations in ambient air and water are low. The average dietary intake is estimated to be about 30-50 µg/day (14), of which only 10% or less is absorbed from the intestines (5). Absorptive rates from the gut can be increased by nutritional deficiencies in calcium or vitamin D or by disorders of iron metabolism. This increase is held largely responsible for the

occurrence of Itai-Itai, a painful cadmium-induced disease of bone found in women from a particular locale in Japan (6). There are roughly 35 µg of cadmium in each pack of cigarettes. Measurements of the amount inhaled in smoke may vary from about 10% to 70% (13) (17). Assuming that the cadmium-containing smoke particles range in diameter from 0.01 µg to 0.5 µg, about half the inhaled dose would be expected to be retained by the lung.

The body eliminates cadmium mostly in urine. Normally this amounts to about 1 to 2 µg/day, so that the total body burden tends to increase with age. To what extent these additional sources of cadmium may contribute to the adverse effects of chronic occupational exposure, particularly involving the kidneys where accumulation of the metal is relatively high, is uncertain. (Cadmium also accumulates in hair; the analysis of hair may be useful in showing that exposure to the metal has occurred, but not to assess the magnitude of uptake (1)).

With chronic exposure to cadmium, nasal passages become inflamed, and there is loss of the sense of smell owing to damage to the olfac-

tory nerve. The teeth show yellow discoloration. How seriously the lungs are affected is a matter of controversy. Several investigators have stated that cadmium causes emphysema (7)(10)(12). A recent study found no evidence to support this concept and indeed questioned its soundness (26). In the latter study, 18 workers who had been exposed for at least 22 years to cadmium dust (average: 32 years) were compared with control subjects in terms of respiratory symptoms, chest films, and a comprehensive battery of functional tests. The two groups were matched in age, height, weight, socioeconomic status, and smoking habits. Since 1972, total cadmium concentrations in the workplace had ranged from 50 $\mu\text{g}/\text{m}^3$ to 356 $\mu\text{g}/\text{m}^3$; while concentrations were presumed to have been higher in earlier years, these data were not accessible. Both groups gave evidence of narrowing of small airways that appeared to be related largely to smoking. The authors concluded that chronic exposure to cadmium "does not represent a major hazard for the lung."

Others have suggested that emphysema cases attributed to chronic cadmium exposure may have resulted from one or more past acute intoxications (14). This would accord with findings in animal experimentation, which show that one or repeated exposures to high concentrations of cadmium chloride may eventually produce an emphysematous lesion (25).

Fibrosis of the lung has been reported among workers chronically exposed to cadmium; this evidence is based on radiographic changes in lung appearance, and a reduction in FVC without any obstruction to flow as measured by $\text{FEV}_{1.0}$ and maximal mid-expiratory flow (MMEF) (24). In animals, cadmium-induced fibrosis is thought to be a forerunner of emphysema by causing distortion of small airways and adjacent parenchyma (25).

Of all organs, the kidney is the most commonly affected by chronic exposure to cadmium. Evidence of renal failure, however, is rare. Proteinuria, comprising both small (molecular weight under 40,000) and large molecules, is not uncommon among exposed workers (13). The percentage affected increases with duration of exposure, approaching unity within three decades (19). It is uncertain to what extent this form of renal injury and the hypertension associated with cadmium intoxication may be related. The association between elevated levels of renal cadmium

at autopsy and a history of hypertension has been reported by several investigators (21).

Anemia and painful demineralization of bone (osteomalacia) have been associated with chronic exposure to cadmium; the latter particularly in association with excessive dietary intake (21). Evidence for an increased incidence of prostatic carcinoma is equivocal (11).

Animal Toxicology

High doses of cadmium chloride aerosol (0.1% solution, aerosol mass concentration unspecified) are injurious chiefly to the bronchioles and adjacent parenchyma (25). There is an acute, edematous reaction, followed by growth of granulation tissue and scarring (25). The scarring distorts and destroys tissue, imparting the appearance of human emphysema of the centrilobular type. It has not been determined whether low concentrations of cadmium aerosols administered over long periods of time may also provoke fibrosis and emphysema in the same species of animals.

Hypertension has been produced in rats with long-term, low-level cadmium feeding, particularly in a species that is genetically predisposed to systolic hypertension (20)(21). The effect is seen in the absence of overt damage to the kidney and may reflect increased reabsorption of sodium by the kidney or a direct effect on the tone of vascular smooth muscle.

Cadmium chloride causes fibrosarcoma when injected into connective or muscle tissue (8). These tissues are mesodermal in origin. The cells implicated in prostatic carcinoma, which was reported to occur more often than expected in one survey of workers exposed to cadmium for a minimum period of one year, is endodermal (specifically epithelial) in origin. Epithelial carcinoma has not been produced in animals with cadmium.

Selenium protects against the testicular necrosis caused by cadmium in animals (6).

Recommendations

Evidence suggests cadmium is more toxic as a vapor than as a particle. Therefore, assurance is needed that air-monitoring methods be sensitive to both physical forms of the metal. This is particularly important in heated environments where the vapor pressure of cadmium may be high.

Enough vexing questions remain concern-

ing the possible adverse effects of low-level, prolonged exposure to cadmium to warrant continued longitudinal studies of exposed workers. The type and severity of lung disease that may occur, and the possible relation between chronic exposure and the incidence of hypertension and of specific types of neoplasm are unresolved.

In animals the nature of the structural and functional changes that may be produced by chronic exposure to low levels of cadmium should be defined more clearly.

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CHLORINE

Introduction

Chlorine is the most abundant halogen and among the most reactive of all elements. It is a yellow-green gas at ambient temperature and liquifies at low temperature (boiling point, 1 atmosphere = -34°C) or elevated pressure (boiling point, 5 atmospheres = 10.3°C). It has a conspicuous, pungent odor, is about 2.5 times heavier than air, and therefore tends to accumulate in dependent sites. Such sites may become extremely hazardous in the event of accidental leaks within confined spaces. Liquid chlorine is a strong irritant that inflames the skin, eyes, and mucous membranes upon contact.

NIOSH has estimated that about 15,000 persons have the potential for exposure to chlorine at work (9). Table VII-3 illustrates the number and variety of these occupations. (Emissions from photographic manufactories may also contaminate nearby community air, as in regions of Niagara Falls, Rochester and Syracuse, New York(9)).

The present federal standard for chlorine is 1 ppm ($\sim 3 \text{ mg/m}^3$), based on an 8-hour time-weighted-average (TWA). NIOSH has recommended a ceiling concentration be established of

0.5 ppm based on a 15-minute sampling period (9).

Acute Exposure, Human

Upon absorption into tissue fluids, chlorine undergoes a series of reactions to produce hydrochloric acid (HCl), hypochlorous acid (HOCl), and nascent oxygen (O). Each of these chemicals damages biologic tissue.

The threshold for detecting chlorine by odor ranges widely among individuals, is inconsistent from one occasion to another and becomes blunted within minutes of the onset of exposure (9). Generally, the average concentration cited in primary references has been under 1 ppm, having ranged as low as 0.012 ppm; at odds with these findings is the statement in the *Handbook of Chemistry and Physics* which states that "As little as 3.5 ppm can be detected as an odor" (7).

The consequences of accidental over-exposure to chlorine gas are well documented, although specific information about the concentrations inhaled by victims is meager. The symptoms and signs associated with acute inflammation of the eyes, entire respiratory system, and skin were enumerated in the Introduction to this chapter. In addition, the teeth may be damaged or discolored. Death may be caused by asphyxia from laryngospasm or massive pulmonary edema. Other nonspecific symptoms include headache, dizziness, anxiety, nausea, and vomiting.

The effects of a single accidental exposure vary in duration. It may be difficult to distinguish between disability arising from psychologic trauma or anxiety and that due to intrinsic respiratory injury. This has been particularly true of retrospective studies carried out on military personnel gassed by chlorine in World War I (5).

Chester et al. could find decreased ventilatory function in only 3 of 55 workers in a chlorine gas plant who had been accidentally exposed one or more times to concentrations in excess of 1 ppm (3). Ambient or background concentrations of chlorine in the plant averaged less than 1 ppm (99% of all samples). Overexposure was defined as an undetermined dose, severe enough to require oxygen therapy. The clinical findings indicated an obstructive ventilatory defect, which cleared rapidly. Earlier, Kowitz et al. described a similar type of obstructive defect in 11 longshoremen hospitalized after an accidental exposure to chlorine, but with a different outcome (8). Here the obstruction increased over the next two years of follow-up. A

Table VII-3
OCCUPATIONS WITH POTENTIAL EXPOSURE TO CHLORINE

Aerosol propellant makers	Iron dezincers
Alkali salt makers	Laundry workers
Aluminum purifiers	Methyl chloride makers
Benzene hexachloride makers	Paper bleachers
Bleachers	Pesticide workers
Bleaching powder makers	Petroleum refinery workers
Bromine makers	Phosgene makers
Broom makers	Photographic workers
Carpet makers	Plastic makers
Chemical synthesizers	Pulp bleachers
Calcium chloride makers	Rayon makers
Chlorinated solvent makers	Refrigerant makers
Chlorinated hydrocarbon insecticide makers	Rubber makers
Chlorine workers	Sewage treaters
Color makers	Silver extractors
Disinfectant makers	Sodium hydroxide makers
Dye makers	Submarine workers
Ethylene glycol makers	Sugar refiners
Ethylene oxide makers	Sulfur chloride makers
Flour bleachers	Swimming pool maintenance workers
Fluorocarbon makers	Tetraethyl lead makers
Gasoline additive workers	Textile bleachers
Gold extractors	Tin recovery workers
Ink makers	Vinyl chloride makers
Iodine makers	Vinylidene chloride makers
Iron detinners	Water treaters
	Zinc chloride makers

Adapted from NIOSH (1976, Table XIII-2)

defect in the diffusing capacity of the lungs, present at the first examination, also worsened. Unlike the workers in the gas plant, the long-shoremen had not worked in an environment characterized by relatively low concentrations of chlorine (< 1 ppm) (3). Whether exposure to low levels of chlorines induces tissue adaptation, which may have contributed to the salutary outcome in the gas plant workers, is unknown.

The following statement appears in another report: "(the) prevailing chemical view is that significant permanent damage does not result from acute exposure to chlorine gas" (11); and the findings in this same study support this viewpoint. Still, a more tenable and prudent view is that while most victims of accidental exposure appear to recover completely, clinically and physiologically, some retain evidence of persistent damage that may even grow worse in time. The importance of factors such as age, previous

state of health, and smoking habits as an influence(s) on the outcome is not yet understood.

Chronic Exposure, Human

Information about the pulmonary hazards of intermittent, long-term exposure to low concentrations of chlorine is ambiguous. Ferris et al. found no difference in respiratory symptoms or ventilatory function between workers in a pulp mill exposed an average of about 20 years to both sulfur dioxide and chlorine and a control group from a nearby paper mill (5). "Considerable self-selection" occurred since many workers who found the odors of the pulp mill disagreeable transferred to the paper mill. Within the pulp mill the men exposed principally to chlorine plus chlorine dioxide had more shortness of breath and slightly lower ventilatory performance than did those exposed principally to sulfur dioxide. The air monitoring was too limited to characterize dosage.

Perhaps surprisingly, both groups showed lower prevalences of respiratory disease than did the male population in the community at large. This finding suggested the workers were not representative of the general population.

The most comprehensive study in North America is that by Patil et al. of 600 workers from 25 plants that manufactured chlorine (10). Concentrations on a time-weighted-average ranged between 0.006 ppm and 1.42 ppm (mean: 0.146 Δ 0.287). Few workers were exposed to over 1 ppm and the average duration of exposure was 10.9 years. Comparison was made with unexposed personnel from the same plant: there was no difference between the two groups in ventilatory function, frequency of colds, shortness of breath, chest pain, abnormal chest x-rays, or abnormal electrocardiograms. The exposed workers tended to report more anxiety, dizziness, and fatigue, and had more tooth decay, which alone among all the parameters tested was interpreted as showing a correlation with dose.

There is no evidence that chlorine is a carcinogen.

Animal Effects

With few exceptions, studies on animals have resorted to lethal concentrations of chlorine. There is virtually no information about the effects of low concentrations of the gas, administered acutely or chronically. An exception is the study of Barrow et al. (2) who exposed mice to concentrations ranging from 0.7 ppm to 38.4 ppm of chlorine for 10 minutes and measured the percentage of change in respiratory rate. This method offers a simple, quantitative means of comparing the irritancy of airborne pollutants. Chlorine slowed the breathing rate, which was judged to be evidence of sensory irritation to the upper airways, particularly the nasal mucosa. (An increase in rate, as occurs with ozone (1), is considered evidence of irritation to the tracheo-bronchial airways and parenchyma of the lung.) The threshold for sensory irritation from chlorine was about 0.9 ppm. This was interpreted by the authors to mean that the current standard of 1 ppm represents an upper acceptable limit.

Recommendations

Accidental exposure to high concentrations of chlorine are likely to recur in view of the ubiquity of the gas. NIOSH should encourage and facilitate the use of sophisticated, follow-up studies of victims, including tests for assessing

the caliber of small airways and the elastic recoil of the lung.

Research undertaken on animals should be directed toward assessing the effects of low-grade, prolonged exposure on the structure and function of the lung. Whatever adaptation to the gas develops with repeated exposures should be determined.

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HYDROGEN SULFIDE

Introduction

Hydrogen sulfide (H_2S) is a colorless gas at ordinary temperatures and liquefies at low temperatures (boiling point = $-61.8^\circ C$) or elevated pressures. The gas is inflammable, explosive and, like cyanide, may be lethal at high concentrations within a few breaths. The soluble salts of hydrogen sulfide are toxic also.

Drilling, mining, smelting, and processing of both fossil fuels and metallic ores, plus a variety of other unrelated industries, may involve hazardous exposure to sulfides. The gas is released whenever sulfur-containing organic matter undergoes decomposition by bacteria. Accordingly, sewers, septic tanks, trucks that transport chemical wastes, fishing boats, fumaroles, sulfur springs and various other settings, may serve as pockets for the gas. About 125,000 workers are estimated to be potentially at risk (8). A partial list of the occupations involved is shown in Table VII-4.

The present federal standard for hydrogen sulfide is 20 ppm (1 ppm = $\sim 1.4 \mu g/m^3$ at $25^\circ C$, 760 mm Hg), described as a "ceiling concentration determined for an eight-hour day" (8). The standard also specifies a peak concentration of 50 ppm not to exceed 10 minutes (8).

Acute Toxicology

The toxicity of hydrogen sulfide is attributable to both biochemical and direct irritative actions. In tissue liquids the gas dissociates into hydrosulfide (HS^-) and sulfide (S^{2-}) ions, which by inactivating a number of respiratory enzymes, interfere with cellular metabolism of oxygen (4)(5)(11). As a consequence, the respiratory center in the brain may cease function, causing apnea and sudden death. Biochemical recovery accompanies the conversion of sulfide to innocuous sulfate ions. As a surface irritant, hydrogen sulfide primarily affects the eyes and respiratory system.

Dose-response relations: Hydrogen sulfide is detectable by smell at about 25 ppb (parts per billion); at 3-5 ppm, the smell becomes offensive (8). The olfactory sense is rapidly fatigued by increasing concentrations of the gas so that the individual is likely to be unaware of continu-

ing exposure.

Inflammation of the cornea of the eye has been reported in workers in Germany exposed to as low as 10 ppm for 6 to 7 hours (8)(10). The simultaneous presence of either carbon disulfide or formaldehyde in the air in these studies may have played contributory roles. A British study associated eye irritation with concentrations of 150 ppm or higher (2). Among the eye symptoms described were pain, blurred vision, and colored halos surrounding light. Inflammation of the conjunctiva and cornea accompanied the symptoms.

There may be evidence of central nervous system stimulation or depression beginning around 200 ppm. At about 500 ppm, hydrogen sulfide produces hypocapnic hyperventilation through stimulation of chemoreceptors in the carotid body, and cardiac arrhythmias (6)(7). At higher concentrations these effects are likely to be disabling; 1,000 ppm can cause apnea within seconds.

Central nervous system involvement may be associated with headache, mental confusion, agitation, dizziness, somnolence, coma, and convulsions (3). There may be nausea and vomiting.

The entire respiratory system may be acutely inflamed. Frothy, at times bloody, secretions may obstruct the airways and require suction or intubation. In one survey, pulmonary edema was reported in 20% of the victims (3). Chest pain, shortness of breath, cough, and cyanosis, are likely to accompany the edema.

A number of case reports of accidental exposure by inhalation have been summarized in the NIOSH criteria document (8). Burnett et al. analyzed in detail 221 cases of acute intoxication among workers in Alberta, Canada. Most occurred in the natural gas, oil, and petroleum industries—typically in confined spaces—and required hospitalization (3). Almost all of the deaths (6%) occurred before hospital arrival. Among the survivors (94%), recovery was complete with little or no evidence of long-term effects. The following have been cited as sequela in other case reports: epilepsy, acoustic nerve damage, and amnesia (8). Burnett et al. also described cases of severe physical injury following loss of consciousness, and drowning has been reported elsewhere (8).

Treatment: Successful treatment hinges on how rapidly the victim is removed from the contaminated environment and supportive measures

Table VII-4**OCCUPATIONS WITH POTENTIAL EXPOSURE TO HYDROGEN SULFIDE**

Animal fat and oil processors	Lithographers
Animal manure removers	Lithopone makers
Artificial-flavor makers	Livestock farmers
Asphalt storage workers	Manhole and trench workers
Barium carbonate makers	Metallurgists
Barium salt makers	Miners
Blast furnace workers	Natural gas production and processing workers
Brewery workers	Painters using polysulfide caulking compounds
Bromide-brine workers	Papermakers
Cable splicers	Petroleum production and refinery workers
Caisson workers	Phosphate purifiers
Carbon disulfide makers	Photoengravers
Cellophane makers	Pipeline maintenance workers
Chemical laboratory workers, teachers, students	Pyrite burners
Cistern cleaners	Rayon makers
Citrus root fumigators	Refrigerant makers
Coal gasification workers	Rubber and plastics processors
Coke oven workers	Septic tank cleaners
Copper-ore sulfidizers	Sewage treatment plant workers
Depilatory makers	Sewer workers
Dyemakers	Sheepdippers
Excavators	Silk makers
Felt makers	Slaughterhouse workers
Fermentation process workers	Smelting workers
Fertilizer makers	Soap makers
Fishing and fish-processing workers	Sugar beet and cane processors
Fur dressers	Sulfur spa workers
Geothermal-power drilling and production workers	Sulfur products processors
Gluemakers	Synthetic-fiber makers
Gold-ore workers	Tank gaggers
Heavy-metal precipitators	Tannery workers
Heavy-water manufacturers	Textiles printers
Hydrochloric acid purifiers	Thiophene makers
Hydrogen sulfide production and sales workers	Tunnel workers
Landfill workers	Well diggers and cleaners
Lead ore sulfidizers	Wool pullers
Lead removers	

NIOSH (1977, Table XIV-2)

are instituted. Resuscitation, including mouth-to-mouth breathing, and establishment of a patent airway may be life-saving.

Nitrites have been shown to be effective in countering the enzymatic effects of sulfide in animals, and in one case of severe poisoning of a worker (12)(13). Nitrite converts the oxyhemoglobin (HbO_2) of red blood cells to methemoglobin; methemoglobin traps toxic sulfate ions forming sulfmethemoglobin; the latter is restored within hours to oxyhemoglobin while the sulfur is excreted in an oxidized state. Nitrites may be inhaled from ampules or injected intravenously.

Oxygen therapy is useful whenever pulmonary edema or depressed ventilation impede the uptake of oxygen by the blood.

Chronic Toxicity

There is little evidence that repeated exposure to low concentrations of hydrogen sulfide causes persistent or cumulative adverse effects. The majority who were exposed to daily levels that could exceed 20 ppm experienced a variety of complaints involving changes in personality, intellect, and memory; eye and respiratory irritation; and gastrointestinal disorders (1). Neurologic changes reflecting damage to the brain or spinal cord were present in the more seriously affected workers. One individual had difficulty in maintaining equilibrium several years following an acute exposure to an unspecified concentration. Sudden and sustained interference with the delivery or metabolism of oxygen by the brain tissue could result in permanent damage.

Animal Studies

Animal studies have been useful in correlating the dose of hydrogen sulfide with lesions produced in the cerebellum, basal ganglia, and cornea; in demonstrating the cardiac malfunction and arrhythmias produced by the gas; and in clarifying the mechanism of hydrogen sulfide toxicity and the palliative effects of nitrites. There is little unambiguous information on the effects that chronic exposure to low concentrations of hydrogen sulfide may have on behavior, vision, the neurophysiologic and cardiorespiratory systems.

Recommendations

A registry of acute hydrogen sulfide intoxication cases should be established, especially those requiring hospitalization. A standardized form of reporting should prove feasible for large

industries. Among the benefits of the registry would be the accumulation of information about the efficacy of different forms of treatment, incidence of persistent clinical disorders, and factors governing prognosis.

Early institution of effective treatment is often critical. All potentially exposed workers should be familiar with proper procedures to be followed and approved methods of resuscitation as well as the danger of rendering assistance in contaminated areas. Consideration should be given to installing first aid units containing ampules and injectable forms of nitrite plus a supply of oxygen close to potentially hazardous settings.

Surveys of workers potentially at risk to repeated exposure to low concentrations of hydrogen sulfide are warranted as are additional animal studies of the potential consequences of long-term exposure of animals to low concentrations.

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MERCURY

Introduction

Three chemical forms of mercury pose occupational hazards: elemental or atomic mercury, inorganic salts, and organic salts. This discussion is confined to the metallic element and inorganic salts.

Elemental mercury, a liquid, vaporizes readily at ambient temperatures. Exposure by inhalation occurs with both the vapor and the inorganic salts as dusts. It was estimated that at least 1,100,000 workers are potentially at risk of exposure to mercury vapor and inorganic salts (10). Their occupations are listed in Table VII-5.

Mercury may also be taken up by ingestion and absorption through the skin. Generally, elimination of the metal from the body proceeds slowly so allowance should be made for cumulative effects from combined occupational and nonoccupational sources. Contaminated fish foods have been incriminated as a source of methyl and ethyl organic mercury.

The standard for inorganic mercury recommended by NIOSH is 0.05 mg/m³ based on a time-weighted-average (TWA) concentration for an eight-hour workday (11). The standard defines "inorganic mercury" to include elemental mercury, all inorganic mercury compounds, and organic mercury compounds exclusive of methyl and ethyl (monoalkyl) salts. There is a National Emission Standard for mercury from stationary sources ranging from 2.3 to 3.2 kg per 24-hour

period depending on the facility or process involved (5); there is no equivalent ambient air standard.

Kinetics, Mechanism of Effect

Following inhalation, mercury vapor diffuses rapidly into the plasma and red blood cells and is distributed to most body tissues (1)(3). The elemental state carries no ionic charge and is soluble in lipids. These properties facilitate rapid passage across cell membranes and localization within nerve tissue (7)(9). Once mercury has been oxidized to a charged ionic state (Hg₂⁺ or Hg⁺⁺), passage across the blood-brain barrier is impeded. The kidney then becomes the principal site for storage and elimination (12).

Largely on the basis of *in vitro* studies, the toxicity of mercury has been attributed primarily to chemical links that are formed with sulfhydryl groups (-SH) present in all proteins (2)(7). Mercury binds with other cellular components also, including amines, phosphoryl, and carbonyl groups. As a consequence, the permeability of cell membranes and the function of a variety of enzyme functions may be altered (8).

Clearance of mercury from the brain is slower than from other tissues. The half-life (time required for one-half to be eliminated) for the total body burden is about two months (6). The extent to which total body burden is reflected in blood or urine concentrations is arguable. Correlations among the concentrations of metal in air (an index of exposure), blood, and urine may be statistically significant for large populations, particularly after chronic exposure to elemental mercury (14), but they break down frequently within individuals. A confounding factor is the tendency for urine concentrations to change on the basis of metabolic activity and diet, independent of body burden. Blood is thought to be a more reliable indicator of body burden than urine (4). There is poor correlation between chronic exposure to inorganic mercury salts and urine concentrations (6).

Mercury is also concentrated in the roots of hair. Since hair tends to grow at a steady rate of roughly 1cm/month the distribution of the metal along the strands of hair becomes a means of relating the magnitude of exposure to specific periods of time. Generally, mercury is about 250 to 300 times more concentrated in hair than in blood (6).

Table VII-5
OCCUPATIONS WITH POTENTIAL EXPOSURE TO MERCURY

Amalgam makers	Fur processors
Bactericide makers	Gold extractors
Barometer makers	Histology technicians
Battery makers, mercury	Ink makers
Boiler makers	Insecticide makers
Bronzers	Investment casting workers
Calibration instrument makers	Jewelers
Cap loaders, percussion	Laboratory workers, chemical
Carbon brush makers	Lampmakers, fluorescent
Caustic soda makers	Manometer makers
Ceramic workers	Mercury workers
Chlorine makers	Miners, mercury
Dental amalgam makers	Neon light makers
Dentists	Paint makers
Direct current meter workers	Paper makers
Disinfectant makers	Percussion cap makers
Disinfectors	Pesticide workers
Drug makers	Photographers
Dye makers	Pressure gauge makers
Electric apparatus makers	Refiners, mercury
Electroplaters	Seed handlers
Embalmers	Silver extractors
Explosive makers	Switch makers, mercury
Farmers	Tannery workers
Fingerprint detectors	Taxidermists
Fireworks makers	Textile printers
Fungicide makers	Thermometer makers
Fur preservers	Wood preservative workers

NIOSH (1973, Table XII-5)

Acute Effects, Humans

Most cases of acute intoxication are either accidental (e.g., following rupture of a large mercury-containing receptacle in a confined space) or the consequence of attempted suicide. If the vapor has been inhaled, the clinical picture will generally reflect injury to the lung (chest pain, cough, shortness of breath) plus general toxemia (fever, chills, profound weakness, anorexia, and joint pain). In nonfatal cases, recovery is rapid and may be complete within 24 hours.

If intoxication follows ingestion of inorganic salts, the site of injury shifts to the abdominal organs. Gastroenteritis (abdominal pain, nausea, vomiting, bloody diarrhea) and renal insufficiency, which may culminate in shutdown, are likely to prevail. Evidence of general toxemia may also be present.

Chronic Effects, Humans

Chronic intoxication chiefly affects the central nervous system. The clinical picture is termed "erethism." Headache and various personality changes are described, including increased irritability, depression, paranoia, insomnia, and loss of memory and mental acuity (2)(13). Mercury may remain unsuspected as the cause of symptoms if the onset is gradual. Motor disturbances also occur. Tremors of the limbs, particularly of the hands, are often an early sign of chronic intoxication. Use of the limb aggravates the tremor. Muscular coordination can become impaired.

Smith et al. found evidence of early erethism in some workers at chloralkali plants where ambient levels of elemental mercury ranged from 0.05 mg/m³ to 0.10 mg/m³ (TWA) (12)(13). At

concentrations above 0.1 mg/m³, tremors and abnormal reflexes occurred with increasing frequency and severity as a function of dose. The authors concluded that dose-response relations below 0.1 mg/m³ were not sufficiently sensitive to warrant concern. (Some unexposed control subjects also had symptoms identified with early erethism.)

Other sites of involvement are the oral cavity (inflammation of the buccal lining and gums, excessive salivation), kidneys (proteinuria, which may lead to the syndrome of nephrosis), skin (rashes), and various changes of a nonspecific nature (anorexia, weight loss, weakness, anemia).

Treatment: Chelating agents, including BAL, d-penicillamine, and dithiocarbamate, have been administered to accelerate the excretion of mercury in urine and sweat. Despite the severe toxicity and disability associated with prolonged exposure to mercury, removal of the patient from the offending environment combined with chemical treatment have at times led to dramatic recovery (16).

Recommendations

The excretion rate of mercury from the body may be modified by metabolic factors. It is not possible to reliably predict the amount of mercury accumulated in an individual from knowledge of air concentrations and time spent in the offending atmosphere (other sources, principally dietary, may also complicate the analysis). Therefore, some method of periodic surveillance of potentially exposed workers should be considered. Admittedly, the earliest evidence of mercurial toxicity is likely to be subjective, even vague. But the appearance of such complaints should merit thorough neurologic examination, combined perhaps with blood and urine analyses.

The ease with which elemental mercury penetrates the placenta and concentrates in fetal tissue should be the basis for protecting pregnant workers from all known exposures to this agent.

Continued toxicologic research into the metabolic, biochemical, and functional changes produced by all chemical forms of mercury, with an eye toward improving the early detection of intoxication, is to be encouraged.

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OSMIUM TETROXIDE

Introduction

Osmium has only limited commercial use. Its principal forms of production are as metallic osmium and osmium tetroxide, also called osmic acid (OsO_4). Osmium tetroxide is toxic. It occurs in crystalline and amorphous states, melts at 40 to 41 °C, and is soluble in water and alcohol. It is highly volatile (vapor pressure at 26 °C = 10 mm Hg); the odor given off is brusque and offensive.

The metal is biologically inert and extremely dense (specific gravity = 22.48). With other metals of the platinum group, particularly iridium, it forms alloys noted for their hardness.

The most recent published estimate of osmium production in the United States is for 1971 and amounts to about 140 lbs. (5). NIOSH has estimated that only about 100 workers are potentially at risk in the production of osmium tetroxide. It is used principally in histology laboratories to fix and stain tissue, and the personnel of these laboratories constitute the principal population-at-risk. The second major use of osmium is in the drug industry as a catalyst in the production of steroid hormones. The alloy has only a small market in the electrical industry and in the manufacture of such miscellany as phonograph needles, engraving tools, and bearings.

The federal standard for osmium tetroxide is 2 $\mu\text{g}/\text{m}^3$ based on an eight-hour time-weighted-average (TWA) and 40-hour workweek. There is no standard for metallic osmium.

The properties that distinguish osmium tetroxide as a fixative are responsible for its toxicity. It reacts with lipids, nucleic acids, and proteins. The structure and function of proteins are

thereby altered. As a consequence, a variety of enzyme systems may be damaged or destroyed (2).

There are more case reports of acute poisoning from osmium tetroxide dating to the last century than the present one. The two principal sources of "new" clinical information are articles by Brunot (1), and McLaughlin and co-workers (3); Brunot's contribution is contained in a footnote to a study on rabbits in which he describes his own symptoms following inadvertent exposure.

Osmium tetroxide vapors irritate the surfaces of the skin, eyes, and respiratory tract. The subject may have smarting of the eyes, lacrimation, and see halos around lights. Corneal ulcers may occur. (A case of blindness was reported in the last century.) Seven workers who were engaged in refining osmiridium and were exposed to vapors estimated to range from 133 $\mu\text{g}/\text{m}^3$ to 640 $\mu\text{g}/\text{m}^3$, developed conjunctivitis that subsided within one day (3).

Among all respiratory irritants, osmium vapors appear to strike with the most dramatic intensity. The odor and sense of nasal irritation are powerful and virtually indistinguishable. Depending on the degree of exposure, all strata of the respiratory system may be involved. Cough has been the most frequent symptom (3). More severe exposure may cause a sense of chest constriction coupled with difficulty in breathing (1).

Headache behind or above the eyes is relatively common (3). The skin may be blackened at the site of contact, owing to reaction of the osmium with lipids.

A therapeutic oddity has been the injection of 1% osmium tetroxide into the joints of patients with rheumatoid arthritis and related disorders (4). The absence of any reported systemic side-effects may be taken as evidence that the action of osmium was confined to the local tissues.

Chronic Effects

No data are available on the possible effects of periodic or repeated exposure to osmium tetroxide among workers who produce it or laboratory personnel who use it.

Animal Toxicology

Acute toxicologic studies on animals confirm the severe, widespread injury to the respiratory system and eyes produced by osmium tetroxide.

Recommendations

The hazard associated with the production and use of osmium tetroxide should be minimal if recommended procedures are followed, caution is observed, and adequate ventilation is provided. No recommendations for research are offered.

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OXIDES OF NITROGEN

Introduction

The term oxides of nitrogen as used in federal occupational standards is reserved for nitric oxide and nitrogen dioxide (23). Both gases are by-products of a variety of combustive processes associated with high temperature. Typically they co-exist together although their relative concen-

trations vary widely, depending on the nature of the combustive process. For example, nitrogen dioxide may comprise over 50% of the mixture formed by a blast of dynamite, but less than 10% of that formed from an oxyacetylene torch (23). Since nitrogen dioxide is the more toxic gas, such variations have important implications for health. Unfortunately, the gases are not differentiated in many reports of occupational exposure.

It is estimated that about one million workers are potentially at risk to repeated exposure of low concentrations of nitrogen oxides (22). A partial list of the occupations is contained in Table VII-6. A small fraction of this total, which includes silo workers, welders, and firefighters, is subject to acute toxicity from sudden high concentrations—or “boluses”—of the gases (10)(21)(27). The general population may be exposed to nitrogen oxides in community air or indoors near gas stoves (24)(31). Tobacco smoke is a source of intense exposure to both nitric oxide and nitrogen dioxide (3).

The present federal occupational standard for nitrogen dioxide is 5 ppm, based on an eight-hour averaging time (TWA). NIOSH has recommended an alternative ceiling concentration of 1 ppm (sampling time unspecified). The occupational standard for nitric oxide is 25 ppm, based on an eight-hour averaging time.

The national ambient air quality standard for nitrogen dioxide is 0.05 ppm (100 mg/m³) annual arithmetic mean.

Toxicity

Mechanism: Comprehensive reviews of nitrogen oxides toxicology are contained in recent monographs and in the criteria document prepared by EPA (12)(24)(29). Several mechanisms

Table VII-6
OCCUPATIONS WITH POTENTIAL EXPOSURE TO OXIDES OF NITROGEN

Braziers	Medical technicians
Dentists	Metal cleaners
Dye makers	Nurses
Fertilizer makers	Organic chemical synthesizers
Food and textile bleachers	Photoengravers
Garage workers	Physicians
Gas and electric arc welders	Silo fillers
Jewelry makers	Sulfuric acid makers

Adapted from NIOSH (1977, p.426)

of toxicity have been postulated, including: (a) combination with water to form nitric acid, a powerful irritant; (b) direct oxidation of lecithin and unsaturated fatty acids, which constitute major elements of cell membranes; and (c) formation of free radicals, which in turn oxidize unsaturated fatty acids in cell membranes and may also denature elastin and collagen, the structural proteins of lung. Nitric oxide and nitrogen dioxide combine with hemoglobin to form a variety of nitroso-hemoglobin complexes and methemoglobin (5). The latter, which is the major end-product, is physiologically inactive.

Acute Effects, Human

As with healthy subjects, patients with chronic bronchitis and asthma have shown little or no functional changes following exposure to 0.5 ppm (15) or 1.0 ppm (13) for several hours; mild irritative symptoms were most frequent among the asthmatics (15). The threshold concentration causing lung function changes in volunteers exposed acutely to low concentrations of nitrogen dioxide is about 1.5 ppm (29). Concentrations in the range of 1.5 to 5.0 ppm may cause the following: narrowing of both central and peripheral airways; stiffening and reduced diffusing capacity of the lung, which probably reflects an abnormal distribution of ventilation and possible swelling of the alveolar-capillary membrane; and a slight fall in the partial pressure of oxygen physically dissolved in arterial blood (P_{aO_2}) without, however, any essential change in the saturation of hemoglobin with oxygen (S_{aO_2}) in either healthy subjects or patients with chronic bronchitis (30). These functional changes may be associated with symptoms of irritation, including cough. Typically, responses are short-lived. There is also evidence that as little as 0.1 ppm of nitrogen dioxide may render the airways in some asthmatic subjects more reactive to carbachol, a pharmacologic bronchoconstrictor (25), but questions regarding the validity of this observation have been raised and confirmation of the experimental results is in order. There is no evidence that low levels of nitrogen dioxide alter the pulmonary functional response to other pollutants, whether gases or particles.

Irritation of conjunctival surfaces has been associated with open arc-welding, in which concentrations of nitrogen oxides were estimated to range from 4 to 20 ppm (21). More massive ex-

posures may cause shortness of breath, cough, weakness, and chest pain, followed by lung edema after intervals ranging from hours to days. Methemoglobinemia may contribute to the hypoxemia associated with both bronchospasm and edema.

With massive accidental exposure, the entire length of the respiratory system may become involved. Pneumonia may supervene; persistent cough and sputum may develop; and inflammation of the bronchioles may progress to obstruction and emphysema-like changes of the neighboring airspaces. While most cases of accidental overexposure recover with little or no apparent functional impairment, the damage associated with obliterative bronchiolitis is likely to be permanent (1)(12). Lethal exposures have been associated with "silage gas poisoning" and with the massive concentrations of nitrogen oxides that may be released by burning plastics and nitrocellulose (11)(18).

Chronic Effects, Human

Information about possible effects of prolonged low-level exposure to nitrogen oxides in industry or in polluted communities is both sparse and equivocal. One study drew the conclusion that workers exposed to nitrogen oxides in a German chemical plant had clinical and laboratory findings consistent with emphysema; the data presented, however, do not appear to support the conclusion (17). Increased rates of respiratory illness, particularly in children living near plants producing TNT in Chattanooga, Tennessee have been attributed to nitrogen dioxide in ambient air (29). Two major criticisms have been directed against these studies, namely that the technique (Jacobs-Hockheiser) used to analyze nitrogen dioxide was unsatisfactory, and that the adverse health effects could have been caused by other ambient pollutants known to have been present. A British study concluded that female children in homes with gas stoves were subject to more respiratory illness than their counterparts in homes without gas stoves. Nitrogen dioxide was suggested as the responsible agent, although no airmonitoring was done (2). This finding has not been confirmed in a more recent study in the United States sponsored by the American Gas Association (19).

Finally, there is physiological and post-mortem evidence for an increased prevalence of emphysema among British coal miners exposed

to "nitrous fumes" from shot firing, particularly associated with the use of Hydrox shells in 1959-60 (14). (The bulk of the charges in these shells consists of nitrates; the shells have been banned from the mines since 1962.) The concentration of nitrous fumes in coal mine headings following shot-firing are reported to range up to several hundred ppm if ventilation is low. Such levels are known to cause severe parenchymal damage in animal lungs.

Animal Effects

Inhalation studies on laboratory animals have provided graphic descriptions of structural lesions that may be produced by acute, subacute, and chronic exposure to different concentrations of nitrogen dioxide, as well as associated biochemical and functional derangements (12)(24) (29). As with other respiratory irritants, the extent and severity of effects are dose-related, so that any anatomic level and respiratory cell type may be subject to injury. Among the effects noted have been impaired clearance of particulate matter, impaired resistance to infection, altered mechanical performance (static and dynamic compliance, resistance of the airways to gas flow), and unevenness in the distribution of ventilation within the lung (4)(8)(9)(16). Which of these functional attributes may be most sensitive to the gas or most likely to show adaptation with repeated exposure is not readily apparent.

Evidence of histologic damage, or of increased capillary permeability that may predispose to edema are seen in rodents at concentrations of about 0.5 ppm (26). Mice exposed to 0.5 ppm of nitrogen dioxide for 3 to 12 months develop bronchiolar inflammation and changes in surrounding airspaces—changes interpreted as being consistent with early focal emphysema (2). Inflammation and thickening of the walls of the bronchioles and alveoli is seen in rats exposed to 2.0 ppm continuously for 33 months and in monkeys exposed to this same concentration for 14 months (6)(7).

There is no convincing evidence that nitrogen dioxide is a teratogen, mutagen, or carcinogen.

Recommendations

Prospective clinical-physiological studies are needed of workers who might be repeatedly exposed to low levels of nitrogen oxides. Emphasis should be given to measurements useful in detec-

ting early emphysema, including lung volume and its subdivisions, small airway function, and when feasible, static lung compliance. A careful assessment of other possible confounding sources of nitrogen oxides, including cigarette smoke, indoor (residential) air, and community air is necessary in such studies.

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Table VII-7
OCCUPATIONS WITH POTENTIAL EXPOSURE TO OZONE

Air treaters	Organic chemical synthesizers
Arc welders	Sewage treaters
Cold storage food preservers	Textile bleachers
Industrial waste treaters	Water treaters
Liquor agers	Wax bleachers
Odor controllers	Wood agers
Oil bleachers	Flight attendants on commercial aircraft

(NIOSH, 1977)

OZONE

Introduction

Ozone (O_3), an allotropic form of oxygen, is colorless, highly reactive, and unstable. Its sources and the populations potentially at risk to its toxic action are diverse. Formed secondarily in photochemical smog, ozone may exceed federal ambient air quality standards with regularity in urban communities and be transported hundreds of miles downwind. (In 1973, maximal hourly average oxidant concentrations equaled or exceeded 0.2 ppm on 100 or more days at air monitoring stations in Pasadena, Pomona, and Azusa, California (17).) Natural sources, represented chiefly by the periodic downdraft of ozone from the stratosphere, may produce ground levels of 0.04-0.05 ppm, with occasional spikes to 0.08 ppm or higher (20). Exposure to stratospheric ozone is most likely to occur in unsealed, high altitude aircraft. Indoor levels may reach about 40-70% of outdoor levels, depending on the type and degree of ventilation in the building and the materials used in furnishings (fabrics adsorb ozone) (1). Homes or offices may generate low levels of ozone intermittently through ultraviolet light and a variety of machines and equipment using high voltages: common examples are electrostatic air cleaners and continuously operated copying machines (1). A listing of occupations associated with exposure to ozone is shown in Table VII-7. It is estimated that about one million workers may be at risk (16).

The federal occupational standard for ozone is 0.1 ppm ($195 \mu\text{g}/\text{m}^3$) based on a time-weighted-average concentration for an 8-hour workday and 40-hour workweek.

The National Ambient Air Quality Standard, based on a maximum one-hour level, has recently been set at 0.12 ppm ($235 \mu\text{g}/\text{m}^3$). The

previous standard of 0.08 ppm was for photochemical oxidants measured as ozone. (Ozone is the major, but not the most reactive oxidant in photochemical smog.)

Effects

Mechanism: Ozone shares similar mechanisms of effect with nitrogen dioxide, a less toxic oxidizing gas. Among the basic modes of biochemical damage postulated for ozone are: oxidation of polyunsaturated fatty acids, especially in cell membranes; formation of free radicals; formation of secondary toxic compounds through oxidation of lipids; oxidation of sulfhydryl compounds (17)(21). Changes in lung mechanics and ventilatory performance may occur reflexly (stimulation of nerve receptors) or through the release of histamine from injured mast cells located in the epithelium of the airways.

Human Effects, Acute

Information about the acute effects of ozone has come from four sources: controlled laboratory studies of volunteers, surveys of workers such as welders, accidents, and studies of the general population exposed to ambient pollution. Under laboratory conditions, the odor threshold is 0.02 to 0.05 (12). As concentration increases between about 0.2 ppm and 2 ppm, symptoms proceed from upper to lower airways and intensify. There may be irritation of the eyes, nose, and throat, substernal tightness, cough, and shortness of breath. (Ozone, however, is not considered responsible for the eye irritation experienced in photochemical smog (21)). Headache and lassitude, suggestive of systemic or a generalized effect, occur occasionally.

The threshold for functional impairment is slightly higher than for symptoms of discomfort. No changes in ventilatory performance (FVC,

FEV_{1.0}) are seen in normal subjects following several hours of exposure to 0.25-0.3 ppm of ozone, to which intermittent light exercise and heat stress are added (8)(21). There are slight average reductions in FVC and FEV_{1.0} at 0.37 ppm of ozone, attributable principally to subjects with evidence of hyperreactive airways which are not statistically significant. Exposure to 0.15 ppm of ozone during vigorous exercise (65% of maximal oxygen uptake) elicits a change in ventilatory patterns characterized by shallow breathing; 0.3 ppm of ozone and vigorous exercise reduce VC slightly but significantly; and 0.3 ppm combined with moderate exercise (45% of maximal oxygen uptake) are associated with wheezing, headache, and other symptoms of discomfort (5). Changes in the lung's mechanical behavior (increased flow resistance, reduced dynamic compliance), and impairment of diffusing capacity are reported at concentrations from 0.45 ppm to 0.75 ppm (21). These effects are generally reversible within hours. Even among normal subjects there may be wide variations in functional response to short-term exposures.

Ozone appears to increase the reactivity of the airways to provocative aerosols such as histamine (7). There is evidence that repeated daily exposure to ozone is attended by diminishing functional effects (tolerance), and that individuals living in Los Angeles, where photochemical smog is commonplace, are less responsive to acute ozone exposure than subjects from regions with little smog (9)(10).

Occupational exposure to concentrations in the range of 2 ppm or higher cause clinical symptoms and signs indicative of pulmonary edema (14). Concentrations of about 10 ppm may be extremely debilitating (13)(15).

Elevated ambient levels of oxidants (of which ozone is considered the most important component) have been associated with increased frequency of headache, cough, eye and chest discomfort among student nurses (11). The threshold for eye irritation, which appeared to be the most sensitive index of response, was estimated at about 0.15-0.19 ppm of ozone, with one-third of the subjects reporting this symptom at 0.5 ppm.

There is epidemiologic evidence to suggest that asthma is aggravated when ambient oxidant concentrations exceed 0.25 ppm (21), and that athletic performance is affected at even lower concentrations (22). The latter is consistent with laboratory findings (5).

Human Effects, Chronic

There is little information on the possible effects of prolonged exposure to low concentrations of ozone, whether among workers or the general population.

One study of shipyard welders exposed to a variety of hazardous pollutants, including ozone, metal fumes, nitrogen oxides, and asbestos, described an increase in residual lung volume suggestive of obstructive airway disease (19). A cohort of pipefitters with little or no exposure to welding fumes or asbestos was used for comparison. The mean ozone concentration to which the welders were exposed was estimated to be 0.10 ppm (range: 0.01-0.36 ppm); the mean nitrogen dioxide concentration was 0.04 ppm (range: 0.01-0.08 ppm). To what extent ozone, among all the pollutants, may have been responsible for the effect is uncertain. An earlier study of seven workers engaged in argon-shielded electric arc welding adduced no evidence of impaired lung function following long-term exposure to 0.2-0.3 ppm of ozone (23). Ventilatory tests of small airway patency and the diffusing capacity, reported to be useful in detecting early emphysematous changes (see Phosgene, (3)) were measured. All subjects smoked cigarettes.

There is no evidence that ozone is mutagenic in humans or that long-term exposure to smog is associated with increased lung cancer mortality (21).

Animal Effects

Considerable research has been done on the effects of ozone on a variety of biochemical systems, cell cultures, and intact animals. The subject is reviewed in two recent monographs (17)(21). Notable among the effects of acute exposure to less than 1 ppm of ozone are changes in the chemistry and function of alveolar macrophages, which imply reduced resistance to infection and impaired clearance of foreign material from alveoli; inflammatory changes, affecting particularly the bronchioles but extending throughout the airways and as far peripherally as the proximal alveoli; and changes in lung function (21). Some of the biochemical toxicity is mitigated by vitamin E (4).

Subacute and chronic exposure may produce changes in the lung akin to aging or emphysema. The primary sites of attack are the bronchioles and alveoli. The bronchioles in rats and monkeys appear to be equally susceptible to mild injury from 0.2 ppm of ozone admin-

istered eight hours daily for seven days (6). Loss of elastic recoil and increased alveolar size have been observed in rats following continuous exposure for 30 days to 0.2 ppm (2). Emphysematous-like changes and thickening of pulmonary arteries have occurred in rabbits exposed 5 days weekly for 10 months to 0.4 ppm (18).

Recommendations

There is need for prospective studies on the possible effects of prolonged, intermittent exposure to ozone on the lungs of workers. This is particularly true of occupations such as welding in which periodic spikes in concentration are likely to occur, since toxicologic evidence suggests that the injurious effects of this gas may be more closely related to peak concentrations than to total dosage (21). (Potentially toxic levels of nitrogen oxides may also be generated during welding.) Such studies should emphasize functional tests that provide information about alveolar elastic recoil and the patency of small airways. Animal experiments suggest that these particular properties are most likely to be affected.

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PHOSGENE

Introduction

Phosgene (COCl_2) is a gas at ambient pressure and temperature; it liquefies at elevated pressure or in cold air (boiling point = 7.5°C at 1 atmosphere). Along with chlorine, phosgene was used as a poisonous gas in World War I. Today, industrially, it has only limited importance despite increasing use in the production of isocyanates.

About 10,000 workers are estimated to be potentially at risk to phosgene (8). A source of accidental exposure is the production of phosgene by decomposition of chlorinated hydrocarbons.

The present federal standard for phosgene is 0.1 ppm (0.4 mg/m^3), based on an 8-hour time-weighted average concentration (TWA). NIOSH has recommended establishment of a ceiling limit of 0.2 ppm (0.8 mg/m^3), not to be exceeded in any 15-minute sampling period (8).

Acute Effects, Human

Phosgene hydrolyzes in the presence of water and biologic liquids to form hydrochloric acid, which is thought to be the basis for its

toxicity (7). Following inhalation, phosgene can be absorbed and cause injury throughout the respiratory system. Liquid phosgene can cause severe internal burns as well as burns of the eyes and skin.

Phosgene imparts an odor said to resemble musty hay. Wells et al. reported that none of a group of military personnel could detect concentrations below 0.4 ppm (1.5 mg/m^3), which is in excess of both the federal standard and recommended ceiling limit (10). About 39% of the group detected phosgene at 1.2 ppm (4.7 mg/m^3), and half could identify the gas at 1.5 ppm (5.9 mg/m^3).

Accidental exposure to phosgene may pass unnoticed since a period of up to several hours can elapse before the onset of symptoms. In addition to respiratory symptoms, there may be evidence of nervous system involvement: dizziness, headache, blurred vision, mental confusion, and muscular twitching. Nausea and vomiting also occur.

The severity of respiratory symptoms varies considerably, depending on the magnitude of exposure. Autopsy reports refer to extensive tissue damage at all levels of the airways and parenchyma (5).

The most detailed examination of the consequences of phosgene exposure is contained in two reports by Galdston and co-workers (2)(3). One was a follow-up study of 6 workers acutely exposed to the gas (2); the second was of chronically exposed workers (3). All 6 workers who were acutely exposed required hospitalization. They complained of cough, shortness of breath on exertion, and chest tightness or pain. Rapid, shallow breathing was a prominent finding. Functional impairment followed no consistent pattern, nor was its magnitude great enough to account for the degree of disability. The authors thought that psychologic factors contributed to the lingering incapacitation. Slight functional defects persisted as long as one year following exposure.

Chronic Effects, Human

The chronic exposures reported by Galdston et al. occurred accidentally in 5 workers over periods of 18 to 24 months (3). This group, in contrast to the acutely exposed workers, showed little evidence of psychologically-related disability. However, functional defects consistent with emphysema, which connote irreversible damage,

were found in four of the subjects; the fifth had normal function. Three of the affected subjects were only 24, 31 and 32-years-old. Information on smoking was not provided.

There have been no published epidemiologic surveys in the United States of workers who might be exposed to low concentrations of phosgene. NIOSH cites a personal communication received in 1974 in which the writer concluded that 326 workers at a plant that manufactured phosgene showed no ill effects ("pulmonary function, lung problems, and deaths related to lung problems") compared with 6,288 nonexposed workers (8). The average concentration of phosgene, determined during a two-month period, averaged 0.003 ppm (0.012 mg/m³) with personal air samplers (20-minute period). With fixed position samples, the majority of concentrations ranged from nondetectable to 0.13 ppm (0.52 mg/m³); a few were offscale, exceeding 0.14 ppm (0.55 mg/m³). Sampling periods were either 20 minutes or 2 hours.

Animal Studies

Animals have been exposed one or more times to a wide range of phosgene concentrations to determine both the threshold of effect and the lethal dose. In one study on rats, there were no significant changes in carbon monoxide (and ether) uptake below a dose of 30 ppm-minutes (Concentration × Time) (3). Above this dose, uptake of these gases was depressed in direct proportion to the logarithmic increase in Concentration × Time. The changes in carbon monoxide uptake were interpreted to represent abnormal distribution of air and reduced diffusion capacity within the lung. Death was seen with increasing frequency above 180 ppm-minutes.

In another study on rats, histologic evidence of injury was found in slightly more than half of the animals exposed to from 13 to 30 ppm-min. of phosgene (6). The earliest lesion occurred in the bronchioles and thereafter extended to alveoli. Higher doses (range: 0.5 to 4 ppm for 5 to 480 minutes) produced a pneumonitis that persisted for months before receding.

Dogs exposed several times weekly (for a total of 30 to 40 half-hour periods, to concentrations ranging between 24 and 40 ppm) developed progressive damage to bronchioles and parenchyma (1). The changes were said to resemble those seen in the development of human emphysema and to be consistent with the functional defects reported earlier by Galdston et al. (3).

Recommendations

It is uncertain whether repeated exposure to low concentrations of phosgene at or near the federal standard has a cumulative effect on the lung, particularly in the small airways and parenchyma. Valuable information could be provided by animal studies that used quantitative methods of assessing functional and structural damage. Conventional tests that are appropriate for industrial surveys can be used to assess small airways function in populations-at-risk. The single-breath carbon monoxide method of measuring lung diffusing capacity is reported to be useful in detecting early emphysema (4) and might prove useful in such surveys. Measurement of the recoiling force of the lung at different lung volumes is not readily performed outside of the research laboratory, but may be invaluable in following small groups of subjects suspected of having emphysematous-like changes.

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Table VII-8
OCCUPATIONS WITH POTENTIAL EXPOSURE TO SULFUR DIOXIDE

Beet sugar bleachers	Ore smelter workers
Blast furnace workers	Organic sulfonate makers
Brewery workers	Paper makers
Diesel engine operators	Petroleum refinery workers
Diesel engine repairmen	Preservative makers
Disinfectant makers	Protein makers, food
Disinfectors	Protein makers, industrial
Firemen	Refrigeration workers
Flour bleachers	Straw bleachers
Food bleachers	Sugar refiners
Foundry workers	Sulfite makers
Fruit bleachers	Sulfur dioxide workers
Fumigant makers	Sulfuric acid makers
Fumigators	Sulfuryl chloride makers
Furnace operators	Tannery workers
Gelatin bleachers	Textile bleachers
Glass makers	Thermometer makers, vapor pressure
Glue bleachers	Thionyl chloride makers
Grain bleachers	Wicker ware bleachers
Ice makers	Wine makers
Meat preservers	Wood bleachers
Oil bleachers	Wood pulp bleachers
Oil processors	

NIOSH (1974, Table XI-2)

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SULFUR DIOXIDE

Introduction

Sulfur dioxide (SO_2) is a colorless gas that is highly soluble in aqueous solution and it imparts an identifiable taste and odor. It liquefies

at high pressure or low temperature (boiling point = $-10^\circ C$); liquid sulfur dioxide is highly corrosive to biologic tissue.

Sulfur dioxide is useful industrially, but it is also an unwanted by-product. About 500,000 workers are estimated to be potentially at risk to the gas (16). A partial list of these occupations is shown in Table VII-8.

Permissible levels of sulfur dioxide have been set for both occupational and ambient atmospheres. The present federal standard for sulfur dioxide in occupational settings is 5 ppm based on an eight-hour time-weighted average (TWA) sampling time (1 ppm = about 2.65 mg/m^3). NIOSH has recommended a reduction in the standard to 2 ppm (16). There are two Primary National Ambient Air Quality Standards for sulfur dioxide: an annual arithmetic mean of 0.03 ppm ($80 \text{ } \mu\text{g/m}^3$) and a maximum 24-hour concentration of 0.14 ppm ($365 \text{ } \mu\text{g/m}^3$) not to be exceeded more than once per year.

Acute Effects

Biochemistry—Mechanisms: All but a small fraction of inhaled sulfur dioxide is absorbed by the liquid lining of the upper airways, particular-

ly during quiet breathing. This fractional uptake may fall significantly—and penetration of the lower airways may therefore increase—during physical activity when ventilatory flow rate is accelerated and mouth-breathing becomes obligatory. Inhaled concentrations of sulfur dioxide in excess of several hundred ppm (toxicological experiments, accidental exposures) may injure the entire length of the respiratory tract and cause peripheral edema.

Following absorption, the gas reacts with water forming a weak acid solution that contains sulfite (SO_3^-), bisulfite (HSO_3^-), and hydrogen (H^+) ions. The relative contribution of these ions to the irritation produced is uncertain. Sulfite oxidase, an enzyme, hastens the conversion of bisulfite to sulfate ions. The latter is non-toxic and is excreted in urine.

Controlled and Occupational Exposures:

Among healthy volunteers acutely exposed to sulfur dioxide, the threshold for changes in respiratory function is roughly 1 ppm. Results from different studies, however, are somewhat divergent. For example, impaired ventilatory function was observed in four subjects exposed to only 0.75 ppm for two hours (6). At 1 ppm, no functional effects were found in one study (21); airway narrowing occurred in 1 out of 11 subjects in a second study (9); evidence of airway narrowing was seen only following 25 maximal breaths in a third study (12). In another study 1 ppm of sulfur dioxide administered during quiet breathing affected the function of both upper and lower airways. Among the effects noted over a six-hour period of exposure were slowing of nasal mucus clearance, narrowing of nasal passages, and progressive reduction in ventilatory performance (4).

More often than not, acute functional responses are short-lived, tending to remit even as exposure continues (15)(17). This applies as well to symptoms of throat irritation and cough produced by higher concentrations of 5 to 15 ppm. Reflex-mediated bronchoconstriction is considered to be the mechanism for narrowing of the lower airways (17). Whether these functional changes are likely to increase or diminish (adaptation) with repeated exposure is uncertain.

In the workplace, concentrations of about 20 ppm may provoke sneezing, coughing, and a choking sensation (16). Fifty ppm may become intolerable after several minutes. A few fatalities have followed exposure to unknown but very

high concentrations of the gas. One report describes a case of chemical bronchopneumonia that ended in death after 17 days (10).

It is debatable whether synergism between sulfur dioxide and airborne particulates has been demonstrated convincingly in human subjects (17); the results to date have been inconsistent (19). The question is important because these two classes of pollutants are found together in a variety of occupations. Animal toxicology suggests that synergism may be expected between sulfur dioxide and some aerosols—especially those capable of catalytic oxidation of the gas to sulfuric acid or in the form of droplets that can absorb the gas (3)(14). (The solubility of SO_2 in the droplet is inversely related to its pH.) Evidence has also been adduced that low concentrations of sulfur dioxide and ozone act synergistically to impair ventilatory function in healthy subjects (6). However, this observation has not been confirmed (7)(8).

Chronic Effects

Epidemiologic studies of workers chronically exposed to sulfur dioxide are summarized in a NIOSH criteria document (16). A recent study, conducted in a copper smelter, points to an accelerated decline in ventilatory performance over a period of one year plus increased cough and sputum associated with exposure to 1.0-2.5 ppm of sulfur dioxide (18). The functional decline was reported to be independent of other pollutants despite the presence of "respirable dust" levels ranging up to 5.4 mg/m^3 (mean = 0.59 mg/m^3), and sulfate levels ranging up to 0.24 mg/m^3 (mean = 0.070 mg/m^3). Concentrations below 1.0 ppm of sulfur dioxide were unassociated with any apparent functional decline. The investigators suggested that continuing exposure to such concentrations of sulfur dioxide could lead to chronic lung disease.

In addition to this prospective study, a second report on the same copper smelter compared exposed workers, employed from less than one year to over twenty years, with a control group from the mine shop (5). Most of the exposure to sulfur dioxide was judged to have fallen between 0.4 ppm and 3 ppm. In general, values for FVC and $\text{FEV}_{1.0}$, expressed as percentages of predicted values, declined with increasing years of exposure to sulfur dioxide. The same trend was seen for cough and sputum. Cigarette smoking appeared to act additively rather than

synergistically with the gas.

Animal Effects

Short-term exposure to sulfur dioxide has been shown to cause airway narrowing in a number of animal species. The narrowing may be of the upper airways (nasal passages), tracheo-bronchial system, or both, depending on the dose and mode of administration. The effect on the nasal passages is due to swelling of the mucous lining and excessive secretions, while that of the lower airways is due primarily to smooth muscle contraction (bronchoconstriction). One investigator has reported finding a slight but statistically significant increase in pulmonary flow resistance in unanesthetized guinea pigs exposed to a mean concentration of 0.26 ppm (range: 0.03-0.65 ppm) (2). This observation has not been confirmed in lightly anesthetized guinea pigs (14). Generally, concentrations in excess of 5 ppm of SO₂ have been required to alter airway caliber or to depress mucus clearance from the lung in animals (16)(20).

Long-term exposures of guinea pigs and monkeys to 0.1-5 ppm of SO₂ have produced little evidence of changes in airway caliber, distensibility, or histological appearance of the lung (1). No synergistic effects were seen when sulfur dioxide was combined with fly ash or sulfuric acid. Dogs may develop some unevenness in inspired air distribution after prolonged exposure to about 5 ppm of gas (13).

Sulfur dioxide does not appear to be a carcinogen (17). To date, one exploratory study suggests that sulfur dioxide may promote the carcinogenic effect of benzo(a) pyrene in rat lungs (11); this possibility has not yet been tested adequately.

Recommendations

The results of one prospective study suggest that repeated exposure of workers to concentrations of sulfur dioxide below the present occupational standard may be injurious to the lung (18). Additional studies of this type which combine air monitoring of other pollutants as well as sulfur dioxide are needed to confirm the observation. The question is important because of the large industrial population potentially at risk.

Whether or not sulfur dioxide is a co-carcinogen is unresolved and should be examined in toxicological experiments (11). The effect of prolonged exposure to a mixture of sulfur dioxide and an aerosol that either absorbs (droplet)

or oxidizes (catalyst-containing) the gas is also recommended. Such a study should include functional tests that are sensitive to changes in both small and large airways, as well as lung morphology at the conclusion of the exposure.

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Table VII-9
OCCUPATIONS WITH POTENTIAL EXPOSURE TO VANADIUM

Alloy makers	Petroleum refinery workers
Boiler cleaners	Photographic chemical workers
Ceramic makers	Textile dye workers
Dye makers	Uranium millers
Ferrovandium workers	Vanadium alloy makers
Glass makers	Vanadium millers
Ink makers	Vanadium miners
Organic chemical synthesizers	Vanadium workers

NIOSH (1977, Table XII-2)

VANADIUM PENTOXIDE

"Vanadium" is a general term that includes the pure metal, chemically combined forms such as the oxides, alloys such as ferro- and aluminum-vanadium, and vanadium carbide. Of these, vanadium pentoxide is probably the most hazardous to health.

The bulk of vanadium extracted from ore is used in metal alloys to harden steel. The pentoxides serve as catalysts for a variety of industrial processes. Approximately 174,000 workers are estimated to be potentially at risk from exposure to vanadium. These occupations are listed in Table VII-9.

Federal standards exist for three forms of vanadium. These standards refer to time-weighted-average (TWA) concentrations for an 8-hour work shift. The standards were originally proposed by the American Conference of Governmental Industrial Hygienists as threshold limit values (TLV) and are as follows:

1. Vanadium pentoxide fume: 0.1 mg/m³
2. Vanadium pentoxide dust: 0.5 mg/m³
3. Ferro-vanadium: 1 mg/m³

The NIOSH criteria document of 1977 recommended the following changes in these standards (4):

1. Substitution of a ceiling limit of 0.05 mg/m³, based on 15-minute sampling periods for vanadium pentoxide, vanadates, sulfates, halides, and other unspecified salts of vanadium. This ceiling is to apply to pentoxide fumes and dusts and is to supersede the present 8-hour standards.
2. The standard for ferro-vanadium is to be maintained as a TWA concentration for up to 10 hours/day, not to exceed 40 work-hour/week.

Acute Exposure, Human

As a trace element, vanadium is an essential component of enzymatic and other biologic systems (2). It usually enters the body in food (7), and in humans is stored mostly in fat and serum lipids. When inhaled in sufficient concentrations, vanadium acts as a direct irritant to the respiratory system. The skin and conjunctiva of the eyes are also affected. The irritant action has been attributed to the acidity of vanadium (pentoxide) in aqueous solution (6). There is evidence that vanadium pentoxide may also be sensitiz-

ing or allergenic (8)(16).

The clinical picture resulting from short-term exposure to vanadium is described in a number of reports (1)(9)(14)(16). Many of these exposures have been accidental, occurring in a variety of activities associated with manufacturing and processing; boiler cleaning has been implicated in several reports. Symptoms may appear within 24 hours of exposure onset.

Irritation of the upper airways is reflected in sneezing, nasal discharge or bleeding, and throat soreness. A green-black discoloration of the tongue has been described (9).

Irritation of the lower airways is reflected in coughing—with or without sputum, wheezing, shortness of breath, chest tightness, and pain. Rhonchi and rales may be heard. In some instances, sulfur dioxide and sulfuric acid may also be inhaled and contribute to the clinical picture. (The irritant effects of the latter agents are not readily distinguishable from those of vanadium; perhaps the best means of weighing their individual effects is through precise air monitoring.)

Conjunctivitis is common. Skin irritation is typified by itching, rash, and eczema. Identification of vanadium in urine has been tried as a means of assessing exposure, but the results have not proven to be a useful correlate of clinical effects.

A single laboratory study involving healthy volunteers is the underpinning for the proposed ceiling of 0.05 mg/m³ (17). Exposure was to vanadium pentoxide particles (98% under 5 μm in diameter) for up to 8 hours at rest. Two volunteers exposed for 8 hours to 0.1 mg/m³ (0.04 mg vanadium/m³) experienced cough with sputum starting 24 hours later and lasting 4 days. Five subjects who inhaled 0.2 mg/m³ (0.08 mg vanadium/m³) developed cough that persisted 7-10 days. In the same study, inadvertent exposure of two subjects to 1 mg/m³ (0.3 vanadium/m³) caused frequent coughing commencing within 7 hours. There were no changes in pulmonary function as measured by spirometry in any subjects. Possible effects on small airway caliber and lung clearance were not tested. (The viability and phagocytic function of alveolar macrophages may be affected by soluble vanadium oxides (12).)

Chronic Exposure, Human

The question of whether long-term exposure to vanadium-containing dust causes or contri-

butes to irreversible lung disease is unresolved. Three epidemiologic studies have been carried out in which the size-distribution and mass concentration of the dusts were assessed.

In the first of these reported studies, which covered a two-year period, workers were exposed principally to vanadium pentoxide at concentrations estimated to range from 0.03 mg/m³ to 5.58 mg/m³ (8). Only 22% of the particles were less than 8 μm diameter. (Particles this large would be expected to deposit principally in the upper airways, trachea, and central bronchi (5).) During this period, symptoms and signs of bronchitis were common. Five of the 36 workers had evidence of pneumonitis. (A clear distinction between infectious and chemical pneumonitis was not made.) Neurasthenia was observed but was considered secondary to the respiratory symptoms and possibly to undesirable features of the workshift. A follow-up report on six of the workers with the most marked respiratory symptoms was made 6 years later (9), when complaints associated with bronchitis were still present. Chest x-rays and spirometric tests provided no evidence of lung fibrosis or emphysema.

The vanadium dusts in the two later studies appear to have been smaller in size range than in the Swedish study (8)(9); hence, these small particles would be expected to have a different, perhaps more peripheral pattern of deposition. Lewis studied workers (average employment 2.5 years) who were exposed, almost without exception, to concentrations of vanadium-containing dust ranging from 0.018 mg/m³ to 0.38 mg/m³; 97% of the particles were under 5 μm diameter (3). About half of the 24 subjects developed productive cough. Lewis described "bronchospasm" in these subjects, which persisted 2 to 3 days beyond the occupational exposure. He concluded that there was no evidence of chronic injury to the lung but performed no functional testing.

Tebrock and Machle studied workers exposed to a vanadium-bearing phosphor that is used to make color television picture tubes (11). Vanadium pentoxide concentrations ranged from 0.02 mg/m³ to 3.2 mg/m³ (mean: 0.844 mg/m³); 90% of the particles collected were under 1.5 μm diameter. Clinical evidence for tracheobronchitis was common. These authors, like Lewis, observed "bronchospasm," which was aggravated with repeated exposure. They also concluded there was no evidence of permanent damage to the lungs, but did recommend

follow-up studies of the workers (3).

In the absence of functional testing in these studies, it would seem prudent to reserve final judgment about the occurrence of permanent lung damage from exposure to vanadium. Sjoberg's study provided findings consistent with central nervous system toxicity; otherwise there was no evidence of systemic effects (8). Earlier, Wyers had reported findings, in workers exposed to vanadium, that he interpreted as evidence of systemic toxicity: elevated blood pressure, palpitation on exertion, and coarse tremors of the fingers and arms, apparently reflecting involvement of the nervous system (15). The manifestations of neurobehavioral toxicity from vanadium are summarized in Weiss (13).

Animal Studies

Studies on a variety of laboratory species confirm the irritant potential of vanadium for the respiratory system. Stokinger found no histologic evidence of lung injury attributable to vanadium pentoxide dust in guinea pigs, rats, rabbits, or dogs after 6 months' exposure to 0.5 mg/m³ (10). There have been no studies of the effects of prolonged exposure to vanadium on lung function, lung clearance, or resistance to infection.

Recommendations

Several questions remain unanswered about the possible hazards posed by soluble vanadium compounds. Whether they may induce immunologic or allergic changes should be defined more clearly. (Are atopic individuals at increased risk?) There is also a need for more precise monitoring data (size distribution as well as mass concentration) and more incisive pulmonary function testing in clinical and epidemiologic studies.

Vanadium's potential for inducing neural and behavioral toxicity should be examined in animal studies. Mechanistic and descriptive types of information are needed. Greater attention should be given to possible neural and behavioral abnormalities in clinical and epidemiological research.

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ACUTE SYSTEMIC EFFECTS OF INHALED OCCUPATIONAL AGENTS

Geoffrey Taylor

DEFINITION

Inhalation of a number of unrelated agents can produce an acute, short-term febrile reaction often associated with myalgia and minor respiratory tract symptoms. This symptom complex has been given many occupationally-related names in the past—brass founders ague, caster's fever, spelter shakes, mill fever, and weaver's cough among others. Causative agents are listed below but are classifiable into three and possibly four groups: a) freshly generated finely particulate metallic oxides, b) combustion products of fluorocarbon polymers and telomers, c) organic dusts containing bacterial endotoxins, and d) (possibly) mycotoxins. Reaction to the inhalation of these agents is similar in many ways. The syndrome may be defined as an acute, short-term, noninfectious, febrile reaction caused by inhalation of the agents below. It is usually associated with general malaise, myalgia, chills, headache, often cough and chest discomfort, and occasionally pulmonary edema. A polymorphonuclear leukocytosis is common as is tolerance to the causative agent after repeated exposure. Chronic effects of the agents are not considered in this section of the report.

LIST OF CAUSATIVE AGENTS

• Metallic fumes (nascent oxides) of the following metals:

aluminum	lead
antimony	magnesium*
cadmium	selenium
chromium	silver
copper*	tin
iron	vanadium
zinc*	

In many reports the metallic fume to which workers were exposed contained several metals and it was uncertain which one or more of the constituents was responsible for the reactions

observed. Those marked with an asterisk (*) have been proven to cause reactions in a highly pure form.

- Combustion products of fluorocarbon polymers and telomers principally:
 - polytetrafluoroethylene
 - fluorinated ethylene propylene
 - polychlorotrifluoro ethylene
 - poly (chlorotrifluoroethylene-vinylidene fluoride)
 - poly (ethylene-tetra fluoroethylene)
 - poly (ethylene chlorotrifluoroethylene)
 - poly vinyl fluoride
 - polyvinylidene fluoride
 - perfluoroalkoxy
 - poly (chlorotrifluoroethylene-vinyl chloride)
 - poly (vinylidene fluoride-hexafluoropropylene)
 - poly (vinylidene fluoride-hexafluoropropylene tetra fluoroethylene)
- Bacterial endotoxin present in organic dusts
- Mycotoxins present in organic dusts. The evidence for toxic effects due to the inhalation of mycotoxins is limited and equivocal.

OCCUPATIONS AT RISK

- **Metal fume fever:**
 - Alloy makers
 - Braziers
 - Electroplaters
 - Foundry workers, particularly brass and bronze
 - Galvanizers
 - Junk metal refiners
 - Metal burners
 - Metal cutters
 - Metal polishers
 - Metal sprayers
 - Metallic pigment makers
 - Shipyard workers

Smelters

Welders

- **Polymer fume fever:**

Fabrication of fluorocarbon polymer products by:

extrusion

moulding

sintering

Solderers, cutters and welders of metal parts coated with or in proximity to fluorocarbon polymers or telomers as in the automotive and electronics industries and in the manufacturing of domestic and laboratory equipment.

- Organic dust fever which may be due to bacterial endotoxin and, questionably, mycotoxins.

probable:

cottonseed oil operators

cotton ginner

cotton textile workers

grain handlers

grain inspectors

weavers

cotton classers and warehousemen

cotton waste utilization workers

possible:

Many theoretically at risk but no data is available. Farm workers, particularly those involved in confinement animal husbandry. Workers in artificially humidified environments as in the manufacturing of synthetic fibers.

EPIDEMIOLOGY

There has been little interest in conducting epidemiologic studies on this group of occupational fevers. This is probably because of their limited duration, relatively nonserious nature, and because tolerance to repeated exposure often occurs. The limited epidemiologic resources available have rightly been devoted to more serious occupational diseases and particularly to chronic nonreversible effects. A classic function of epidemiologic studies is to relate prevalence of disease to exposure and from this to determine dose-response relationships. This is particularly difficult in the group of occupational fevers for two main reasons. First, as tolerance to exposure often develops and no objective residua are detectable, investigators must rely on questionnaire information—seeking a history of work related febrile illness, often years in the

past. This is unreliable and easily confused by the worker with an infectious illness. Prospective studies of new workers which might alleviate this problem have not been reported. The second problem, relating to the dose, causes great difficulty because of the complexity of the occupational environments in which this group of conditions occur. Metal fumes invariably contain the oxides of several metals; polymer fumes are highly complex and vary considerably with the temperature at which they are generated; both endotoxins and mycotoxins occur together with a vast array of other complex substances in organic dusts. The limited data which are available provides no dose-response information and should be considered relatively unreliable as far as the disease prevalence is concerned.

Many reports of metal fume fever state that the condition is "common" among new workers but do not give further information. Brodie, in a study of an unspecified number of welders in shipyards, stated that 20% had chills and fever occasionally while 5% had frequent episodes (19). Bachelor et al., investigating disease in workers handling finely divided zinc oxide and sulfide, produced a similar proportion (6). They found that 9 of 24 workers reported reactions and of these, three had occasional and one frequent recurrences. In a more thorough study by Ross, 530 welders aged 20 to 59 were interviewed and 116 (22%) reported a history of metal fume fever (94). Many of these workers related their symptoms to welding galvanized metal, particularly in an enclosed environment. Exposure to finely divided copper dust generated while polishing copper plates was investigated by Gleason (48). He implied that all exposed individuals suffered symptoms and that these were prevented by reducing the concentration of copper from between 78 to 120 $\mu\text{g}/\text{m}^3$ to 0.8 $\mu\text{g}/\text{m}^3$. Fumes generated from ferro-chrome alloys produced symptoms in 20 of 40 tappers who were highly exposed while only one of 30 less exposed workers in the same plant reported problems (106). These studies only give a rough indication of prevalence and provide no information on the response to different exposure situations.

There is also minimal epidemiologic data on the prevalence of effects due to pyrolysis products of fluorocarbon polymers. In a study of 77 workers in a small PTFE fabricating plant, Polakoff et al. found that 60 (86%) had experienced febrile reaction at some time and that

14 (18%) reported multiple episodes in the previous year (91). The observation that most of the reported episodes were more than a year in the past suggests the possibility of the development of tolerance. Concentrations of PTFE particulates were in the range 0-2.4 $\mu\text{g}/\text{m}^3$, but decomposition products were not measured.

A prevalence of 47% (14 of 30) was observed by Adams in workers processing PTFE (1). Some environmental sampling was carried out, but no conclusions can be drawn as to dose-response. Multiple episodes of fever were reported; the majority of the reactors were smokers. This relationship between smoking cigarettes and polymer fume fever has been stressed in many reports. Wegman and Peters found 7 of 13 workers exposed to a heated liquid fluorocarbon telomer, used in the production of synthetic crushed velvet, gave histories of polymer fume fever (118). All affected workers were cigarette smokers. Many authors considered the smoking of cigarettes accidentally contaminated by fluorocarbon polymers to be an important route of administration. Dose-response studies using contaminated cigarettes were reported by Clayton (26). He observed that smoking one cigarette contaminated with a minimum of 0.4 mg of tetrafluoroethylene telomer would produce a pyrexial illness and that approximately the same amount was required on a cumulative basis in which cigarettes each contained 0.05 mg. It is likely that ill effects due to smoking contaminated tobacco are responsible for a large proportion of polymer fume fever cases. This is clearly important in its prevention.

Reported prevalences of pyrexial illnesses induced by organic dusts differ greatly. This is not surprising due to the marked variability of such dusts and the subjective way in which data are collected. There is no dose-response information even at the level of total or respirable dust, nor have symptoms been related to the concentration of endotoxin in the dust. Indeed, though it is likely that endotoxin is important in generating fever in individuals exposed to organic dust, this is not proven. It has recently become possible to measure endotoxin using the sensitive *Limulus* amoebocyte lysate test (30). Although this test may give positive responses with other substances (37), these are not likely to be present in the occupationally important dusts. Olenchok and Major reported levels in grain dusts of the order of 0.4 $\mu\text{g}/\text{gm}$ (87). Kutz et al.

obtained a similar concentration in cotton dust (65). These values are probably more reliable than previous estimates of 3 to 11 mm/gm in cotton dust measured by Pernis et al. using other less sensitive methods (89). Even assuming high concentrations of whole dust in the working environment, the dose of endotoxin taken in during an eight-hour shift might be of the order of 0.1 μg . If this estimate is correct, it is debatable whether such a small amount would induce pyrexia when inhaled. This raises the possibility that other agents present in the dust might be important.

In early reports of mill fever in the cotton textile industry, it is implied that febrile reactions are common among new employees; prevalences are not reported. Prevalences of pyrexial illnesses in new workers, ranging from 10% to 50%, were reported in 37 cottonseed oil mills studied by Ritter and Nussbaum (92). In the cotton textile industry Werner found that 26 of 414 cardroom operatives suffered febrile illness (120). Schilling obtained a similar prevalence of 7.2% in a study of 528 workers (96). The latter author noted that a prior occurrence of mill fever had no relationship to the later development of byssinosis. Similar variation has been reported in grain handlers' fever. These have varied from a high of 18 out of 55 (32.7%) reported by Kleinfeld (64) to a low of 6 out of 441 (1.4%) reported by Broder et al. (20). Even in a situation in which extreme exposure to endotoxin occurs, not all workers suffer illness. Of 30 workers exposed to an aerosol of dried sewage at total dust levels up to 4 mg/m^3 , only one-third had febrile reactions (70). Though endotoxin concentration is not known, heat treated dried sewage must be very rich in endotoxin. This again indicates the need for further work on the relationship of endotoxin to occupational pyrexial illness. Other workers, particularly in farming, are exposed both to endotoxins and mycotoxins. No epidemiologic information is available.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The group of conditions discussed in this section are usually short-term pyrexial illnesses which are self-limiting and often only occur following initial (few) exposures in a proportion of new workers. Though the symptoms may be temporarily incapacitating—and with high exposure, may result in pulmonary edema—no ob-

jective evidence of the illness remains and no permanent impairment has been reported. Prevalence data based on questionnaires have varied greatly from study to study. No reliable prevalences are available which are representatives for the total exposed population.

Because tolerance develops rapidly with exposure to organic dusts (endotoxin) and to metal fumes, only new workers or those who have avoided exposure for some time are at risk of developing symptoms. The proportion of the total work population truly "at risk" is therefore indeterminate. It is debatable whether tolerance to fluorocarbon polymer pyrolysis products occurs. NIOSH estimates that 5,000 workers are potentially exposed and may all be at risk of developing symptoms.

PATHOLOGY

Short-term pyrexial reactions of an influenza-like nature consequent to occupational exposure have been recognized for many years. Thackrah gave a clear description of metal fume reactions in 1832; Arlidge described the pyrexial reaction to dust in the textile industry, "mill fever," in 1892. Despite this early recognition, there is very little systematic research on the pathology and pathogenesis of these pyrexial reactions following respiratory tract exposure. There are many studies of bacterial endotoxin reactions. Stemming initially from the development of injection therapy in the latter part of the 19th and early part of this century, research concentrated on injection effects rather than respiratory tract exposure. Mycotoxin research is more recent, but again respiratory tract exposure has been relatively ignored because the effect of mycotoxin ingestion in spoiled food was the overriding concern. The effects of fume inhalation from heated fluorocarbon polymers was first recognized in 1951 (53), but research into the mechanisms of the acute reaction is scanty.

Syndromes produced by diverse agents are similar. All involve a lag period of several hours between exposure and first effects; all involve a neutrophil leukocytosis and pyrexia; all are usually self-limiting, resolving within approximately 24 hours. Symptomatology of "aches and pains," chills shivering, general malaise, headache, cough, and other respiratory tract symptoms (and sometimes nausea and vomiting) are common to all. Especially interesting is the development of a tolerant state on repeated exposure. This is clearly documented with repeated ex-

posure. This is clearly documented with repeat exposure to endotoxin and metal fumes and has been demonstrated in rabbits to the particulate component of polytetrafluoroethylene fumes (24). There are not studies on possible tolerance to mycotoxin exposure.

Metal Fume Fever

In a series of five papers in 1927 and 1928, Drinker and his colleagues from the Harvard School of Public Health presented the first thorough experimental studies of metal fume fever in humans and animals. They reproduced the syndrome with very pure zinc fume inhalation in normal volunteers. They observed a polymorphonuclear leukocytosis commencing between 2-½ and 5-½ hours after inhalation, reaching a peak at about 9-½ hours, and lasting for about 36 hours. They demonstrated temporary decreases in vital capacity but no changes in chest radiography (107). They demonstrated tolerance to zinc fume exposure on consecutive days and noted that a leukocytosis did not occur on the second exposure (34). The same group also showed that finely divided zinc oxide powder (0.4 μ in size) and magnesium fumes produced the same effects (35). Drinker & Drinker studied the effect of zinc and magnesium fumes on cats, rats, and rabbits (32), and confirmed an earlier observation: rather than a pyrexia, a fall in temperature resulted (112). They also demonstrated an outpouring of polymorphonuclear leukocytes into the airways. Vigliani and his group were able to induce fever in rabbits by exposing them first to an aerosol of dilute acetic acid, followed by zinc oxide fume (89). Control rabbits exposed to acetic acid alone did not develop fever. They demonstrated tolerance on repeated exposure and showed that this did not cross-tolerate to bacterial endotoxin. They were able to demonstrate endogenous pyrogen in the serum of exposed rabbits and postulated that the mechanism of metal fume fever involved the direct liberation of leukocyte endogenous pyrogen by metallic oxide [see review by Atkins, 1960 (4)]. They noted that on histologic examination, the pulmonary capillaries of zinc-exposed rabbits were filled with polymorphs. Hence a close contact between zinc fume and leukocytes was possible. Ohmoto et al. also demonstrated the pyrogenicity of zinc and a variety of welding fumes in the rabbit (85). In this series of experiments the fume was given intravenously as a suspension. They were able to show the development of tolerance to zinc fume after two

doses, at weekly intervals, but failed to show tolerance to welding fume which contained metals other than zinc. They were unable to induce fever with commercial zinc oxide, metallic zinc, the coating materials of the welding electrodes, commercially available iron oxides (ferrous and ferric), and oxides of manganese, silicon, aluminum, magnesium, and cadmium. This work, therefore, provides evidence that metallic oxides must be nascent (i.e., freshly generated) to induce fever.

The same group of workers demonstrated that the pyrogenic component of welding fume was present in the particulate portion of a watery suspension (86). It was thermostable in suspension. It became inactive when desiccated by heat but not when desiccated by lyophilization. This suggests that either particle size or crystal structure might be important in the induction of fever.

In following up this work, Mori et al. showed the pyrogenicity of zinc, lead, and magnesium fumes on inhalation by rabbits depended on the presence of carbon monoxide in the fume (77). Only small amounts (less than 0.01%) of CO were necessary. Leukocytosis occurred both with and without the presence of carbon monoxide in the fume. The authors suggest the reaction of carbon monoxide with the metallic oxide results in the formation of a catalytically active N-type semiconductor. This (they suggest) is the component of welding fume which induces the fever. McCord speculated on the possible immunologic causation of metal fume fever and tolerance induction (71). He suggested an immune response to a metal proteinate as the causal mechanism with an antibody as the mechanism of tolerance. There is no evidence to support this hypothesis and it is immunologically unconvincing.

Summary

The pathogenesis of metal fume fever involves the induction of a peripheral blood and airways leukocytosis by an activated or nascent metallic oxide. The mechanism for this is not known. There is evidence to suggest that fever results from the liberation of endogenous pyrogen, probably from leukocytes. The mechanism of tolerance is not known, but cross tolerance to endotoxin does not occur in rabbit experiments.

Polymer Fume Fever

The products produced on heating this group of substances depend primarily on the temperature and environment in which the reaction takes place. At lower temperatures the monomer from which the material is produced is the principal product. At higher temperatures a range of perfluoro compounds containing 3-5 carbon atoms and a particulate fume with a particle size of 0.2-0.5 μm is found. At still higher temperatures carbonyl fluoride is produced. This compound readily hydrolyzes to hydrogen fluoride and carbon dioxide in the presence of water vapor. Many other pyrolysis products have been identified in smaller amounts. A review of the pyrolysis process and products produced is presented in the 1977 NIOSH criteria document for a recommended standard for occupational exposure (80).

Harris first described the clinical picture of polymer fume fever (53). He noted its similarity to metal fume fever but did not document a detailed investigation. He noted that in cases reported to him by a colleague, a leukocytosis had been present. Because of the similarity to metal fume fever, Harris analyzed PTFE ash and sublimate for metals. He concluded that metals could not be responsible. Bruton was the first to suggest the smoking of cigarettes accidentally contaminated with fluorocarbons was an important means of exposure (22).

A detailed investigation of an inflight illness in 35 individuals by Nuttal provided more information (83). He traced the illness to PTFE incorporated in asbestos tape wrapped around an exhaust manifold. This vaporized because of the heat of the manifold. He confirmed the occurrence of a polymorph leukocytosis with an increase in young forms both in the aircraft passengers and in one volunteer experimentally exposed to heated tape.

Chest radiographic changes, which resolved within 72 hours, were described by Robbins and Ware (93). These were found within a few hours of exposure to heated PTFE. Changes consisted of bilateral diffuse infiltration which the author interpreted as pulmonary edema. Evans reported further evidence of pulmonary edema on chest x-ray in a worker who used an oxyacetylene torch to dismantle a metal table contaminated

with a tetrafluoroethylene telomer (40). The x-ray changes resolved completely over a seven day period.

Exposure to one of the perfluoro breakdown products (perfluoroisobutylene) in laboratory workers was reported by Makulova (67). The duration of exposure was brief (less than one minute), but the concentration was not known. As perfluoroisobutylene is only one of many trace products produced by heating fluorocarbons (116), it is likely that exposure to the pure compound was more intense than usually received in the workplace.

All five patients exposed to perfluoroisobutylene showed x-ray changes developing within 4-6 hours. In four patients, the changes were consistent with pulmonary edema, but the fifth had multiple small opacities. One patient died; the autopsy findings were of pneumonia and pulmonary edema with a hemorrhage in the left adrenal. This patient had suffered from pneumonia two months before exposure and this could conceivably have made her more vulnerable. These several reports of pulmonary edema are cause for concern, suggesting that polymer fume fever is not always the benign, short-term pyrexial illness most consider it to be.

There have been a number of experimental studies on whole polymer fume effects on animals and of selected components thereof. These have demonstrated that at high concentrations, pulmonary edema, pulmonary hemorrhages, and death are produced (23)(24)(97) (116). Production of leukocytosis in animals has proved to be difficult as in the case with metal fumes. Cavagna et al. reported both pyrexia and leukocytosis, preceded by a decrease in body temperature, with the same technique they had used in their metal fume fever studies (24). They preceded the inhalation of PTFE fume by an inhalation of dilute acetic acid. They were also able to induce fever by the intravenous injection of washed fume particulate and by this route induced a tolerant state. As in the case of metal fume fever, there was no induced crossed tolerance to *E. Coli* endotoxin. Blagodarnaya confirmed pyrogenicity of the particulate phase of PTFE fume (14), however, washing the particles or storing them for six months abrogated this response. Further evidence supporting the importance of the fumes' particulate phase is provided by Waritz and Kwon (116). They found removal of the particulate by filtration abolished

mortality and pulmonary pathology in rats. Filtration did not significantly reduce hydrolyzable fluoride levels; they were in the range where the presence of particulates causes pathology and death. Thus filtration reduced mortality from 6/6 to 0/6. They suggested the particulate carried toxic products into the alveoli, because the particle size range was 0.5-2 μ m. In view of the conflicting results using washed particulate, this question is still undecided.

Summary

Polymer fume fever is similar to metal fume fever; it involves peripheral blood and airways leukocytosis following the inhalation of the particulate phase of fluorocarbon polymer fume. Radiographic evidence of pulmonary edema has been reported in some human cases and has been produced on intense exposure in animal studies. Unlike metal fume fever, tolerance to repeated exposure is not clearly documented in man, however, it has been demonstrated in rabbits with repeated intravenous injection of a fume particulate suspension. The participation of endogenous pyrogen in the febrile response has not been demonstrated but was postulated by Cavagna et al. based on the synchrony of leukocytosis and fever and on the degranulation of polymorphs after phagocytosis of particles *in vitro* (24).

Organic Dust Fever—An Endotoxin Effect?

Medical science has been interested in the effects of endotoxin, for a variety of reasons, since the latter part of the 19th century. Initial research was stimulated by the observation that injection of a variety of substances, particularly by the intravenous route, would induce fever and various symptoms of an influenza-like nature. Injected materials included distilled water, saline, therapeutic agents such as salvarsan, colloidal metals, and bacterial vaccines. Reactions were eventually traced to the presence (in the solutions) of heat stable pyrogens of bacterial origin (58)(98). Research continued (a) because of the possible therapeutic value of induced fever in such conditions as neurosyphilis, gonorrhoea, and other diseases (54), and (b) because of the growing use of bacterial vaccines in the prophylaxis of disease. Further research into bacterial pyrogens derived from the use of Coley's fluid in the treatment of cancer (81). Basic research into the mechanism of fever provides an abundant literature on the effects of bacterial pyrogens as they

are a ready means to induce febrile reactions in experimental animals. Recent research has been devoted to the role of endotoxin in human shock, particularly in relation to abdominal surgery in poor risk patients.

Bacterial endotoxin has been suggested as a cause of a variety of occupational disease conditions. These include mill fever, weaver's cough, mattress makers' fever, bible printers' fever, humidifier fever, byssinosis, grain fever, bag-assosis, farmer's lung, and others (90). Some of these occupational illnesses have been subsequently shown to be due to other agents—notably bagassosis and farmer's lung (see section on Hypersensitivity Pneumonitis)—while the case for the role of endotoxin in the etiology of byssinosis is poor (see section on Byssinosis). Two major problems exist when attempting to relate occupational health data with the large body of literature on endotoxin. 1) In the occupational setting, endotoxin enters the body by the respiratory tract, whereas virtually all endotoxin research has involved the injection route, usually intravenously. 2) Of even greater difficulty, is that in the workplace endotoxin is invariably present in dust associated with an array of many other complex substances. This makes determination of the specific effects of endotoxin difficult or impossible.

Endotoxins are characteristically present in gram-negative bacteria. They form an integral part of the organism and unlike exotoxin are not secreted by living bacteria. They are released from the organism on death and autolysis. Originally studied by Boivin and Mesrobeanu (15) and consequently often referred to in early literature as Boivin antigens, they have a molecular weight of between 10^6 and 10^7 daltons (110). Endotoxin is stable on storage and heating, requiring about two hours at 160°C for inactivation. It is more labile in alkaline solution (9). Endotoxins are made up of a complex of phospholipid, polysaccharide, and protein. The phospholipid, lipid A, is responsible for the toxic and pyrogenic effects of endotoxin; the polysaccharide carries the principal immunogenic determinants specific for the organism from which it was derived. The determinants are made up of small numbers of hexose or pentose units and endotoxin from a single species may have several such determinants. Because of this, cross reactivity between species is common. The sugar

determinants constitute the somatic or "O" antigens of the microorganism. Lipid A in isolation has low toxicity because of its insolubility. It regains toxic activity when conjugated to a carrier molecule as in its natural state (11). The detailed structure of endotoxin is reviewed by Morrison and Ulevitch (79).

When given intravenously to humans or experimental animals, endotoxin produces a characteristic sequence of events (4)(11). Fever develops within 15 to 50 minutes and may be biphasic in character—giving peaks at approximately $1\frac{1}{2}$ and 3 to 5 hours. The character of the temperature curve depends on the dosage given. Pyrogenic reactions are readily produced in man, horses, dogs, cats, and rabbits, while guinea pigs, rats, and mice may fail to respond or may develop mild hypothermia. Associated with the fever are changes in the formed elements of the blood. If a sufficient dosage is given, an initial leukopenia precedes the pyrexia. This is followed by a leukocytosis involving mainly an increase in the number of immature granulocytes. A transient thrombocytopenia has also been reported. In man, the fever is associated with headache, myalgia, chills, and general malaise. Larger doses given to experimental animals result in peripheral vasodilation, visceral hemorrhages, shock, and death. These effects are produced by intravenous administration; the intramuscular and subcutaneous routes lead to slower and decreased responses, and in some reports, to absence of effect.

Only a limited amount of information is available on the effects of inhaled endotoxin. Pernis produced fever and dyspnea in less than 10% of rabbits exposed to an aerosol generated from a solution of $15\ \mu\text{g}/\text{ml}$ (90). This occurred with latency of 30 to 50 minutes. If the rabbits were given repeated doses with intervals of at least two days, a high portion responded with fever and dyspnea. The same group of workers (25) were unable to generate either fever or leukocytosis in rabbits given an aerosol generated from $10\ \mu\text{g}/\text{ml}$ of endotoxin. Using an extremely large dose, Snell did produce reproducible pyrexia in rabbits, however this was associated with leukopenia (103). Snell used an aerosol generated from $0.5\ \text{mg}/\text{ml}$. It is difficult to equate the inhalation dosage received by the rabbits with doses which would produce significant responses intravenously. Rabbits will produce pyrexia when given doses in the range of 0.0001 to $0.0003\ \mu\text{g}/\text{kg}$ (4).

The rabbits in all these experiments received at least these small amounts by inhalation.

A number of studies have exposed human volunteers to endotoxin by inhalation. Neil et al., investigating an outbreak of an acute illness among rural mattress makers, isolated a gram-negative bacterium from stained cotton (82). They subjected three volunteers to a culture filtrate of this organism for a ten minute period. They responded by cough, chest tightness, headache, generalized aches and pains, and irritation of mucous membranes. There was a latency of about 45 minutes to 1½ hours and a leukocytosis with a predominance of young forms. Symptomatology lasted for approximately 24 hours. Studies of pulmonary function were not carried out. Although there undoubtedly would be endotoxin in the seven-day culture filtrate, it is impossible to know at what level this would be present. Pernis et al. also exposed man to endotoxin (90). They used concentrations of 20 µg/ml and obtained slight fever, a dry cough, and shortness of breath. The same group of workers exposed normal individuals to 40 to 80 µg of endotoxin total (25). They obtained neither pyrexia nor leukocytosis. However, two of eight of the normal individuals had a significant fall in FEV₁, and one of three individuals with chronic bronchitis also had increased airways resistance. On a weight-for-weight basis, man is more sensitive in his response to endotoxin than is the rabbit. Thus, 0.0005 to 0.002 µg/kg will promote a rise in temperature (4). This means the average man will respond to appreciably less than 1 µg on intravenous injection. It would seem likely that in all these human studies, more than this dose would enter the respiratory tract. As the work of Trejo and LiLuzio (111) and that of Mori et al. (76) suggests that lung tissue does not have great potential for the detoxification of endotoxin, it must be assumed that either endotoxin is bound locally without producing systemic effects, or that it enters the body rather poorly from the respiratory tract.

There is sparse literature on the histopathology of endotoxin inhalation effects and no studies on the pathogenesis of the changes observed. Using repeated doses, over a five month period, Snell described the development of bronchitis and bronchiolitis (103). He suggested the possibility that hypersensitivity, presumably to the polysaccharide portion of the endotoxin, was

responsible. Cavagna et al. also described similar changes and again related them to a hypersensitivity mechanism, rather than to a primary toxic effect (25). These authors also demonstrated changes in lung mechanics, primarily an increase in airways resistance and tachypnea, after repeated, prolonged exposure. These studies postulate the possible implication of endotoxin inhalation in chronic obstructive pulmonary disease. They do not provide information on acute toxic effects. Single exposures to endotoxin in guinea pigs and hamsters were studied by Hudson et al. (59). They demonstrated polymorph recruitment into the airways, with platelet aggregations in small pulmonary vessels adjacent to bronchioles, and evidence of leukocyte diapedesis from blood to airways. Changes were not found in the alveoli.

There is a vast literature on the pathology and pathogenesis of changes which occur following intravenous administration of endotoxin. It is to this body of work that we must look for pathogenetic mechanisms, but with many reservations. There are several reasons for cautious extrapolation: It has already been noted that there is a considerable species variation in response; therefore, effects observed in animals may be irrelevant in man. Targets for endotoxin effects are numerous and complexly interrelated; targets hit and activated depend on the dose given. Effects produced by a big dose (e.g., diffuse intravascular coagulation) are not seen with smaller doses. To confound the dosage effect still more, preparations of endotoxins vary considerably in toxicity and sometimes in their ability to initiate some pathways of toxicity. For example, the ability to activate the complement pathway is dependent on molecular weight while some aspects of toxicity are not (45). As has been already noted, when administered by inhalation, endotoxin is, in order of magnitude, less toxic than when given parenterally. This suggests that accessibility to target sites is impaired when given by the respiratory route. Finally the complexity of responses to endotoxin and the interrelationships between multiple effector pathways make the determination of which is primary, secondary, or tertiary difficult to interpret.

There is considerable literature on the Shwartzman phenomenon (101). Basically this involves the "preparation" of a tissue (usually the skin) by local injection of endotoxin, followed several hours later by intravenous challenge. A

local hemorrhagic lesion results. Agents other than endotoxin can both "prepare" tissues and elicit similar reactions. Because this phenomenon seems to be unrelated to febrile illnesses induced by organic dusts, it is not considered further.

Endotoxin appears to be able to interact with any cell, possibly by virtue of the affinity of the hydrophobic portion of the complex for cell membranes (99). Earlier literature abounds with descriptions of necrosis of many tissues—gastrointestinal, reticuloendothelial, liver, heart, bone marrow, kidneys, and others when a large dosage of endotoxin is administered to animals (9). These gross changes are probably irrelevant in the context of the inhalation route of administration.

Target cells of greatest importance at lower doses are neutrophil polymorphs, platelets, endothelial cells, and possibly macrophages. Endotoxin also interacts with certain plasma proteins. It is able to activate the Hageman factor (clotting factor XII) and thereby has the potential to activate the blood clotting sequence and also the kallikrein-kinin system (39). It is also able to activate the complement cascade, either the classical pathway (involving antibody reacting with determinants on the polysaccharide moiety) by the classical pathway in the absence of antibody via lipid A (29), or by directly activating C_3 in the absence of antibody [the alternate pathway of complement activation (47)]. The polysaccharide part of the molecule is responsible for alternate pathway activation (78). Complement activation by either pathway results in the production of C_3 and C_5 anaphylotoxins with their capacity to induce an acute inflammatory response via chemotaxis, lysosomal enzyme release, and the secretion of histamine from mast cells. Increases in serum histamine caused by endotoxin have been demonstrated *in vivo* (56) as have increases in serum lysozyme content (57). However, doubts as to the importance of the reactions of endotoxin with complement are raised by the work of Ulevitch and Cochrane. They showed that though prior depletion of C_3 in rabbits prevented the early reversible thrombocytopenia and hypotension on administration of endotoxin, the later phase of endotoxin effects and lethality were not influenced (113). These authors suggest the main effects of endotoxin are caused by the direct action of the lipopolysaccharide on peripheral blood cells, endothelial cells, and possibly other cells. Other work, using a similar approach, con-

flicts with this suggestion and implicates C_3 and terminal complement components in lethality (21). The studies of Johnson and Ward suggest that C_3 and possibly more terminal components, are protective against endotoxin induced lethality (60). There is still a need to define the role of complement activation in endotoxin-induced injury.

Platelets and granulocytes have a high affinity for lipopolysaccharide (105). Radio-labelled endotoxin given intravenously is rapidly bound, mainly to cells in the peripheral blood buffy coat and the liver (16)(17). Changes in the peripheral blood cells are usual in endotoxin effects. Within minutes of administration, a leukopenia is produced, followed several hours later by a leukocytosis mainly involving an increase in young polymorphs. A transient thrombocytopenia is also common and this can be followed again several hours later with a more prolonged fall in platelet count. The decrease in these blood cells is associated with their sequestration in the pulmonary blood vessels and in the sinusoids of the liver and spleen (4)(11). The mechanism causing this sequestration by the lung is not known but may involve effects of endotoxin on vascular endothelium (5). Ralis et al. also suggest that lysosomal enzyme release from granulocytes would produce lung injury. The doses they used were high (4 to 6 mg/kg); it is unlikely the extreme changes they describe would be produced by small quantities of inhaled endotoxin. Other workers have shown that endotoxin binds to endothelial cells (108), and that overt damage can result (46). This could initiate either blood clotting mechanisms, the release of agents such as prostacyclins which have been shown to be present in endothelial cells (66), or promote the attachment of peripheral blood cells.

Of major importance in the reaction of endotoxin with granulocytes is their release of endogenous pyrogen. As has been noted, fever is characteristically found in some species (including man) when endotoxin is administered. Much research has been devoted to investigating this phenomenon. The initial work of Beeson (7)(8) and Bennett(10) demonstrated the release of endogenous pyrogen, principally from granulocytes by endotoxin. This low molecular weight protein rapidly produces a monophasic rise in temperature without inducing leukocytosis. It is present in serum following administration of endotoxin and may be demonstrated by passive

transfer to other animals (4). Recently, endogenous pyrogens have been shown to be present in macrophages (51). The mechanism of endogenous pyrogen action is either directly or indirectly on the temperature regulating center of the hypothalamus. It has been suggested that prostoglandin E (PGE) may be released by endogenous pyrogen, and it is this substance which induces fever by action on the hypothalamus (102). In addition, prostoglandins of both E and F series have been shown to be released into the circulation in endotoxin shock (27)(62). It is, therefore, possible that release of PGE by endotoxin from any cell could contribute to the pyrexia without the intervention of endogenous pyrogen.

In addition to the prostoglandins, histamine, and bradykinin already mentioned, other vasoactive agents have been shown to be released by endotoxin. They include 5-hydroxytryptamine (3), catecholamines (84), cholinergic agents (115) and angiotensin (52). Whilst these agents may be important in endotoxin shock together with the possible direct effects of endotoxin on the heart and autonomic nervous system (55), their importance following the inhalation of small doses of endotoxin is debatable. Of this list of vasoactive substances, the prostoglandins may be the most important in relationship to the lungs. Parratt and Sturgiss provide good evidence to support this view (87). They pretreated cats with either a prostoglandin synthetase inhibitor or a prostoglandin antagonist and found that both the pulmonary and systemic hemodynamic effects of endotoxin were prevented. Their work also suggested neither histamine nor 5-hydroxytryptamine were of major importance in these effects. Additional research which supports the importance of the prostoglandins is the pyrogenicity of PGE (102). The observation that PGE is chemotactic to polymorphs (61) and that PGE given intravenously to human volunteers caused headache, an oppressive feeling in the chest, facial flushing, and abdominal cramps also suggests this group of lipids may be important in endotoxin-induced occupational fever. Prostoglandins of the F series also have potent effects. Thus, PGF_{2α} is a potent bronchoconstrictor (by inhalation in man) while PGE₂ is a bronchodilator (69). Fifteen-methyl-substituted PGF_{2α} has been administered as an abortifacient, and respiratory problems, a neutrophil leukocytosis, and a decreasing platelet count have all been observed (119). It is difficult to interpret the

changes in neutrophils, as similar changes are observed during normal labor, however, many of the less serious effects of endotoxin administration can be mimicked by administration of these biologically active lipids.

A further effect of endotoxin which could be relevant to respiratory disease and possibly to the inhalent route of administration was shown by Shimizu and Mahour (100). They demonstrated a significant decrease in pulmonary surfactant, following a single intravenous dose of endotoxin in rabbits. Endotoxin could gain access to surfactant-producing cells in the peripheral airways by inhalation; thus this observation deserves to be pursued.

The other agents demonstrated to be released by endotoxin do have the capacity to produce pulmonary changes, particularly by effects on airways smooth muscle. Direct evidence to support this hypothesis, and indeed the role of prostoglandins in inhaled endotoxin effects is lacking. Studies of intravenous endotoxin effects reveal many possible pathogenic mechanisms which could theoretically operate when endotoxin is inhaled. Which, if any, are important is still unproven.

The phenomenon of tolerance to endotoxin pyrogenic effects was first observed by physicians using these agents for therapeutic purposes. Studies to investigate the mechanisms involved have been carried out in both animals and man. Earlier literature on tolerance is extensively reviewed by Bennett and Cluff (11) and Atkins (4). With daily injections, suitable animals species cease to give the expected temperature curve after about the fourth dose. Initially, there is a lengthening of the latent period and a decrease in the second fever peak. This is followed by a decrease, but often not the total disappearance, of the first fever peak. Other aspects of endotoxicity—lethality, shock, and leukopenia—are also diminished. It should be emphasized that tolerance is a relative state and a much larger dose of endotoxin will cause effects even in a tolerant animal. Tolerance persists in animals for about two weeks.

Tolerance in man is similar but has only been demonstrated by intravenous administration. Fever diminishes progressively and is usually absent or minimal by about the fifth or sixth daily dose. Tolerance is associated with a decrease and eventual absence of the unpleasant symptoms of endotoxin administration, although a

mild headache may persist. It should be noted that though the initial transient leukopenia does not occur in the tolerant human, subsequent leukocytosis is not prevented. The proportion of induced young polymorphs decreases, and the duration of the leukocytosis may decrease. Other blood changes noted in man include a transient decrease in mono-nuclear cells and in lymphocytes (42)(72)(75).

It is difficult to determine from the literature the precise length of time during which human tolerance persists after cessation of endotoxin administration. Morgan interrupted administration of endotoxin for up to five days with no decrease in tolerance, however, he showed that tolerant individuals again became sensitive between four and five weeks after the last dose (75). Interruption of the daily administration of endotoxin for two days had no effect on the progressive downward trend of pyrexia in studies reported by Mechanic (72). It is likely that the tolerant state persists in man for about two weeks.

Earlier studies into the involved mechanisms showed that tolerance to endotoxin obtained from one species of microorganisms would induce tolerance to an unrelated one (4). In addition, there appeared to be no correlation between specific circulating antibodies and tolerance; pyrogenic reactions could be induced when tolerance had disappeared even though antibodies persisted. This lack of correlation between agglutinating antibodies and tolerance was also shown to be the case in man (42)(75). An immune precipitate of antibody and endotoxin was shown to be pyrogenic to animals (74); passive transfer studies from tolerant rabbits produced only a mild degree of tolerance (41). All these studies tended to indicate that immunologic mechanisms were not involved in tolerance. The successful induction of tolerance in immuno-suppressed rabbits supports this view (31).

The work of Beeson provided an alternative mechanism (7)(8). He demonstrated that reticuloendothelial blockade, using thorotrast or trypan blue, would largely remove tolerance, and that these blocked animals had retarded removal of endotoxin from circulation. He also showed that tolerant animals remove endotoxin from the blood more rapidly than nontolerant animals. He suggested that tolerance was due to an enhanced capacity of the reticuloendothelial system to remove and detoxify endotoxin. Other workers provided evidence to support this

hypothesis. Biozzi et al. showed that endotoxin caused an initial nonspecific decrease in reticuloendothelial function followed by augmentation (12). Braude et al. using radiolabelled endotoxin, showed more rapid removal of the radioactivity from the circulation and increased uptake in the liver (18). Even in tolerant animals there was considerable binding of the radiolabelled endotoxin to peripheral blood cells. They noted, however, that even in animals which had spontaneously lost tolerance, the rate of endotoxin clearance from the circulation did not return to control levels. Following up this observation, Braude and Zalesky showed that smaller doses of endotoxin were cleared at equal rates in normally intolerant animals, thus casting doubt that augmented uptake by the reticuloendothelial system was important in tolerance at other than very high doses (18). Freeman further investigated the role of the reticuloendothelial system in tolerance (44). He noticed that the timing of changes in reticuloendothelial function did not agree with the changes in endotoxin response, and he was able to demonstrate the involvement of humoral factors in tolerance. However, these appeared not to be specific and he did not consider them to be immune in nature.

Other workers persisted in evaluating the possibility of immune mechanisms. The cross reactivity of tolerance was further investigated by Watson and Kim (117). They showed cross tolerance did occur between endotoxins obtained from some pairs of species and not between others. This is acceptable from an immunologic viewpoint because immunologic cross reactivity is common in bacteria. They also showed that tolerance induced by suspensions of lipid A cause only slight tolerance to the whole complex, while tolerance induced by the whole endotoxin molecule gave tolerance to lipid A. These investigators suggested that immune mechanisms were important in tolerance induction, but that the immunogenic determinant involved was not the somatic "O" antigen. It should be noted that it was antibody against just these determinants which had been measured in previous studies. In studies of rabbit tolerance, Greisman et al. provided evidence for two mechanisms: one could be abolished by reticuloendothelial blockade and was nonspecific; the second and more important, was humoral and endotoxin specific (49). The same group also investigated tolerance in man (5). They showed human tolerance to endotoxin

was not associated with increased reticuloendothelial activity as measured by the clearance of radiolabelled aggregated human serum albumen. They were also able to transfer tolerance using plasma and were able to break tolerance by giving half a dose to which the man was tolerant, followed by the other half two hours later. Radiolabelled endotoxin was also cleared more rapidly in tolerant subjects. These observations together with the fact that dermal reactivity to endotoxin was greater in tolerant than nontolerant volunteers (i.e., a hypersensitivity phenomenon) all suggest that an immune mechanism is involved in tolerance induction. The work of Kim and Watson supported this view with pig studies (63). They showed that colostrum deprived piglets were more sensitive than their colostrum fed litter mates and that the antibody responsible was probably in the IgM class. They also showed (in other species) that the specificity of the antibody was not against the somatic "O" antigens and that tolerance could be induced using endotoxin obtained from mutant organisms which did not possess "O" antigens. The evidence for antibody mediation of tolerance, therefore, seems sound. Differences of opinion expressed in the literature probably stem from the marked differences in dosage and purity of endotoxin preparations used, together with possible species variation.

Possible Effects of Mycotoxin Inhalation

Mycotoxins are toxic products produced by a wide variety of fungi. They vary greatly in chemistry, but the detailed structure of many of them is known. Major interest in mycotoxins has been in their ability to produce disease in animals and man when ingested. The classical poisoning of man by ergot alkaloids, produced by the fungus *Claviceps purpurea* growing on rye, is well known as is the carcinogenicity of aflatoxin B₁. Because, except under adverse conditions, man tries to avoid eating spoiled food, many of the mycotoxicoses have involved the poisoning of domestic animals. The toxicology of mycotoxins is thoroughly reviewed by Uraguchi and Yamazaki (114).

There is limited information on the effects of inhaled mycotoxin. Emanuel et al. (38) also citing Samsonov (95) suggested that the inhalation route may be important. They described ten patients who were exposed to massive fungal inhalation in silos. A pyrexial illness with chills,

cough, and irritation of mucus membranes occurred with a latent period of several hours. Leukocytosis was common and chest x-ray changes suggesting diffuse interstitial disease were found in several patients. All recovered after an illness of from several days to a month. A biopsy of one patient's lung showed a multi-focal acute inflammatory process related to terminal bronchioles, alveoli, and interstitial tissue. These areas contained many fungal spores. The authors were unable to define which fungus was responsible, although they isolated at least five species. Because they could not demonstrate immunologic responses to any of a wide range of fungi and because the clinical picture was different from hypersensitivity pneumonitis, they ascribed the disease to fungal toxins.

There are no published accounts on the effects of mycotoxin inhalation in experimental animals. Unpublished studies from our laboratory (104) have investigated the effects of T₂ toxin given by the intratracheal route. T₂ toxin is a trichothecene toxin produced by *Fusarium* species which was one of the species of fungus isolated from the patient reported by Emanuel et al. No pulmonary pathology was induced by non-lethal doses of 50 and 100 µg. Destruction of rapidly dividing cells in the gastrointestinal, reticuloendothelial, lymphoid, and testicular tissue was, however, produced. More research is needed on the inhalation effects of this group of potent toxins.

CLINICAL DESCRIPTIONS

The symptomatology of the group of conditions included in this section are similar and will be considered together. After a latent period of from one to eight hours, the exposed individual develops a fever with chills, headache, myalgia, and general malaise. Respiratory tract irritation, with cough and chest discomfort, is common but not invariable; dyspnea is sometimes present. Sweating is often a feature; nausea, abdominal discomfort, and sometimes vomiting occur, particularly with polymer and metal fume exposure. The symptom complex lasts usually for up to 24 hours although the individual may feel unwell for a longer period of time. Pulmonary edema produced by fluorocarbon polymer fumes has taken about one week to resolve. If mycotoxins are accepted into this group, even longer is required for recovery. The intensity of reaction appears to depend on dose; a larger dose pro-

duces more severe effects with a shorter latency. This particularly applies to fluorocarbon polymer fumes. A sweet or metallic taste is often reported by individuals with metal fume fever.

Apart from pyrexia, physical signs are often completely absent in mild cases. In some patients, evidence of respiratory effects may be present in the form of moist sounds and occasionally rhonchi heard over the chest. There is sometimes evidence of mucosal irritation with redness of the conjunctivae and pharynx. Physical signs of pneumonia have been rarely reported following metal fume inhalation and pulmonary edema with polymer fume fever.

The disease is self-limiting. Moreover, repeated exposure may lead to a tolerant state. This is common in such conditions as mill fever for which endotoxin is considered responsible. Tolerance does occur to metal fume exposure, but symptoms of metal fume fever may recur if the individual is either exposed to a particularly high concentration or avoids exposure for a period of time. Tolerance to polymer fumes has not been clearly reported but probably does occur (see Epidemiology subsection). The effects of repeated exposure to high concentration of mycotoxins has not been studied.

There are no specific test for this group of diseases. Pulmonary function tests may be entirely normal or may reveal evidence of mild airways obstruction. Chest x-ray changes suggestive of pulmonary edema have been occasionally described in polymer and metal fume fever; changes suggestive of diffuse interstitial disease have been described following mycotoxin exposure. Otherwise, chest x-ray is usually normal. There is almost invariably a polymorph leukocytosis in the peripheral blood, usually with an increased proportion of young forms. Studies on polymorph airways recruitment in human airways are limited; it is possible this might provide a useful test. Fishburn and Zenz suggested measurement of the pulmonary fraction of lactic dehydrogenase could be useful in metal fume fever (43). This has not be confirmed.

There is no specific therapy for this group of diseases; in most situations, after overnight bed rest a patient will be recovered. Aspirin is useful because of its antipyretic and analgesic actions. Other more unusual complications such as pulmonary edema should be treated by appropriate methods. The acute disease invariably recovers, however, chronic toxic effects do occur

with some of the agents, e.g., cadmium. These can clearly carry a totally different prognosis from those of the acute disease, but consideration of long term effects is not within the scope of this section.

DIAGNOSTIC CRITERIA

There are no specific diagnostic criteria for this group of occupational fevers. The key to their recognition is physician awareness of their existence and the taking of a careful and detailed occupational history. Symptomatology is similar to that of many virus infections from which they need to be differentiated. Unless virus isolation or serology are carried out, there are no specific ways in which they can be differentiated. The results of virus isolation or serology are slow and reliance must be placed on clinical judgment. Helpful points in differentiation are that virus infections are usually longer lasting; often produce greater evidence of respiratory tract damage than occupational fever; and may not be associated with a polymorph leukocytosis, at least in the early stages.

METHODS OF PREVENTION

The prime method is the prevention or limitation of exposure to fumes and dusts which cause the febrile reactions described. This should be achieved primarily by engineering controls with adequate exhaust ventilation directed toward the source of the agent. This is particularly relevant in welding and cutting operations in confined spaces. Respirator use should be limited to temporary situations where high concentrations of an agent are inevitable. Adequate house-keeping of a plant will minimize exposure. Polymer fume fever has been frequently related to the smoking of contaminated cigarettes. This source can be avoided by forbidding smoking in risk areas and the provision of facilities for adequate personal hygiene before the worker leaves such areas. Environmental standards recommended by NIOSH are largely based on chronic effects; dose-response data is lacking with respect to pyrexial reactions. It is, however, likely that with respect to metal fumes and cotton dust, recommended standards will prevent or considerably minimize febrile reactions. Because of their complexity, NIOSH has not considered environmental standards for the breakdown products of fluorocarbon polymers to be practical; reliance has instead been placed on good work practices

and engineering controls. It is probable that the current OSHA standards for grain dust which is grouped as a "nuisance dust" is not sufficiently low to prevent grain fever. There is need for reconsideration of this standard.

RESEARCH NEEDS

There are four major gaps in our knowledge relating to this group of conditions: what is the responsible agent within the complexity of the fume or dust; how does it induce fever; what are the dose-response relationships in previously unexposed individuals and in repeatedly exposed workers; and are any currently unrecognized long-term effects induced. Even metal fumes contain several metals and which is responsible for pyrexial illness is in many cases not known. Organic dusts from cotton or grain are incredibly complex and variable and it is only by inference that microbial toxins are considered to be important. These research gaps will be very difficult and costly to close and because of the nature of the conditions involved, will inevitably have a low priority for funding.

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SECTION VIII
NEOPLASMS

OCCUPATIONALLY INDUCED LUNG CANCER EPIDEMIOLOGY

Richard A. Lemen

INTRODUCTION

It has been estimated that lung cancer will kill approximately 77,000 men and 28,000 women in the United States during 1981 (16). This accounts for 34% of all types of cancer deaths in males and for 15% in females. It is expected that 122,000 new cases of lung cancer will occur in the United States in 1981. This will account for a total of 22% of deaths in males and 8% of deaths in females. The age-adjusted lung cancer death rates have increased steadily in men from 5 per 100,000 deaths in 1930 to about 70 per 100,000 deaths in 1980. In females, the rate did not climb as steadily: from 2 to 3 per 100,000 deaths in 1930 to about 7 to 8 per 100,000 deaths in the mid-sixties. However, from the mid-sixties to 1980, the rate has increased rapidly to approximately 18 per 100,000 deaths. It has been suggested that the rapid rise in lung cancer among females is because of the increasing number of women in the work force and because many more women have taken up smoking (128).

ASBESTOS

Occupational Exposure—Historical Studies

In 1935, 55 years after the usage of asbestos was introduced on a large-scale basis in industry, suspicion of an association between asbestosis and lung cancer was reported by Lynch and Smith (75) in the United States and by Gloyne (38) in the United Kingdom. About 10 years later, case reports of pleural and peritoneal tumors associated with asbestos began to appear (144)(145)(149). Epidemiologic evidence from Doll showed a tenfold risk of lung cancers in the U.K. asbestos textile workers who had been employed from 1930, that was prior to regulations that were written to help workers improve dust conditions in factories (27). Similar findings were

reported in the United States in 1961. Mesotheliomas were also detected, but this fact was not published until later (81)(119). Possible variations in risk with other types of asbestos fibers were rarely considered in the earlier reports. Since 1964, following the recommendations of the UICC Working Group on Asbestos Cancers (UICC 1965)(136) for new studies, there has been an expansion of epidemiological studies in many parts of the world.

Epidemiologic Studies—Lung Cancer

Mixed Fiber Types

In most industrial processes different fiber types are mixed, so that pure exposures to a single asbestos type are rare. Mortality studies of defined populations of asbestos manufacturing, insulating, and shipyard workers have provided the most concrete evidence concerning the association between bronchial cancer and exposure to asbestos. Reports received from several countries: England (30)(92), Germany (12), the United States (118), the Netherlands (129), and Italy (112) have confirmed this evidence.

Elmes and Simpson (31) have extended their earlier report (30) to include deaths occurring since 1965 through 1975. The mortality trend has shifted from a preponderance of asbestosis and gastrointestinal deaths to malignancies from lung cancer and mesothelioma, (diseases associated with longer latent periods). These authors report that their findings would suggest any standard based "on the prevention of asbestosis, may not provide adequate protection against neoplasia."

A sevenfold excess of lung cancer was found in a group of insulation workers who had been exposed to chrysotile and amosite asbestos, but not crocidolite (121). Enterline and Henderson reported a 4.4 times increased risk of (respiratory cancer) mortality among retired men who had

worked as production or maintenance employees in the asbestos industry and who had been exposed to mixed fibers (32). Among men with mixed fiber exposure (crocidolite and chrysotile) in the asbestos cement industry, the rate was 6.1 times the expected rate. In a British naval dockyard population, Harries showed that there had been an increased rise in mesotheliomas since 1964 (43). However, the full biologic effects of asbestos in shipyard workers would not have been expected to be detected until the 1970's and thereafter (117).

Edge reported that shipyard workers with mixed asbestos exposure and pleural plaques (without evidence of pulmonary fibrosis) had a 2.5 times increased risk of developing carcinoma of the bronchus, when compared with matched controls without plaques (29). In a study of sheet-metal workers with measurable and mixed asbestos exposure, an excess of deaths from malignant neoplasms (24.7% of the deaths for two cohorts, selected for 5 or more years, who worked in the trade; with 19.1% of deaths for a group where 14.5% was expected) was largely attributed to an excess of malignant tumors of the respiratory tract (21). Of the 307 deaths in the first cohort, 32 lung cancer deaths were significantly in excess (1.7 times the expected level).

Weill et al. reported on the mortality experience of a cohort of 5,645 men employed in the production of asbestos cement products and who had at least 20 years since first exposure (146). These workers were exposed largely to chrysotile with some crocidolite and amosite. Among this group, 601 persons were identified as deceased by the Social Security Administration. The vital status of 25% was unknown, and were assumed to be alive, which probably resulted in underestimation of the true risk. Death certificates were obtained for 91% of the known dead. Dust exposures were estimated, using each worker's employment history in conjunction with historical industrial hygiene data.

Weill et al. observed increased respiratory cancer mortality only among those with exposure in excess of 100 mppcf-year, where 23 cases were observed vs. 9.3 expected (146). The unusually low SMR for all causes in the low-exposure groups suggests the possibility of a selection bias and any interpretation of risks at low exposures should be done with caution. Separating the cohort by fiber type exposure, the authors concluded that the addition of crocidolite to chryso-

tile enhanced the risk for respiratory malignancy; however, an excess risk was observed among those not exposed to crocidolite with cumulative exposures in excess of 200 mppcf-months. Both average concentration of exposure and duration of exposure were found to be related to cancer risk.

McDonald and McDonald studied the mortality of 199 workers exposed to crocidolite during gas mask manufacture in Canada from 1939 to 1942 (84). This cohort was followed through 1975, when by this time 56 deaths occurred. Out of these 56 deaths, 4 (7%) were from mesothelioma and 8 (14%) from lung cancer.

Chrysotile

McDonald et al. reported an increased risk of lung cancer among men employed in Quebec chrysotile mines and mills (85)(86). The risk of lung cancer among those workers most heavily exposed was five times greater than those least exposed.

Kogan et al. investigated the cancer mortality among workers in asbestos mining and milling industries between 1948 and 1967 (54). The total cancer mortality rate among workers was 1.6 times higher than that found in the general male population; for female workers the rates were 0.8 times higher for those in mines and 1.1 for those in mills. The lung cancer risk for male miners and millers was twice that of the general male population. For females in mines and mills, the risks were 2.1 and 1.4 times that of the general female population, respectively. For workers over 50 years of age, the risk of lung cancer was greater: for men in mining, 4.0; those in milling, 5.9; for women in mining, 9.5; and those in milling, 39.8 times that found in the general population.

Wagoner et al. reported on the cancer risk among a cohort of workers in a major manufacturing complex utilizing predominantly chrysotile asbestos in textile, friction, and packaging products (143). An excess of respiratory cancer occurred among asbestos workers in each duration-of-employment category down to and including one through nine years. They observed statistically significant standard mortality ratios of 122 for all malignant neoplasms of the respiratory system. The asbestos workers in this study were located in the area of predominantly Amish dutch population with known low frequencies of smoking. The authors, nevertheless,

used the general white male U.S. population as a control group, which most likely resulted in an underestimation of the degree of risk.

Robinson et al. (106) reported an additional 8 years of observation and 385 deaths to the Wagoner et al. (143) study of mortality patterns of workers among one facility manufacturing asbestos textile, friction, and packing exposed predominately to chrysotile. Except for 3 years (during World War II), chrysotile constituted over 99% (per year) of the total quantity of asbestos processed. During those 3 years, amosite was selectively used to a limited extent because of Naval specifications and accounted for approximately 5% of the total asbestos used per year. Crocidolite and amosite (for the other years) accounted for less than 1% of the total usage in very selected areas. Exposures to these two types may have played a role in the etiology of disease; however, due to the overwhelming exposure of the cohort to chrysotile, it is likely that the other exposures played a minor role in the overall mortality patterns. Robinson et al. confirmed the observations of Wagoner et al. that statistically significant excess deaths were due to bronchogenic cancer.

Weiss reported no unusual mortality experience over a 30-year period for a cohort of workers employed in a paper and millboard plant, reported to be using only chrysotile (147). The author concluded the study results were suggestive of a minimal hazard from chrysotile. This conclusion must be viewed in light of the limitations inherent in the study. First, the population studied was small ($n = 264$) and only 66 workers had died at the time of the analyses. Moreover, the unusually low SMR for many of the contrasts in the Weiss et al. paper suggests the possibility of a selective bias greater than usually seen when contrasting industrial populations are contrasted with the general population.

Enterline and Henderson found that retired men who had worked as production or maintenance employees in the asbestos industry, and had been exposed only to chrysotile, and who had reached 65 years of age, had a respiratory cancer risk 2 to 4 times greater than that expected (32). Among men within the asbestos cement industry exposed only to chrysotile, a one- to four-fold excess of respiratory cancer was found.

Anthophyllite

In Finland, anthophyllite mining has been associated with an excess bronchial cancer risk

of 1 to 4 times the overall expected and about double this figure for those with more than 10 years' exposure time (53)(87)(88).

Synergism

There is marked enhancement of the risk of lung carcinoma in those workers exposed to asbestos who smoke cigarettes (11)(25). Hammond and Selikoff interpret the excess lung carcinoma risk from asbestos in nonsmokers to be small (41). No link between cigarette smoking and mesotheliomas has been observed in a prospective study by Hammond and Selikoff (41). A preliminary study on female workers employed between January 1940 and December 1967, in a predominantly chrysotile asbestos textile plant, revealed 7 lung cancer deaths among 580 women when only 0.63 deaths were expected ($p < 0.01$) (64). One lung cancer death was observed in a smoker, two in women of undetermined smoking history, and four in women who "never" smoked cigarettes (as determined from hospital admission charts).

It is important to note that the historic documentation of cigarette consumption patterns is lacking for most retrospective cohort studies done on asbestos workers. It is also important to note that a sizable portion of the general population, the group usually selected for comparison in these studies, are cigarette smokers. Therefore, the risk of lung cancer demonstrated for these industrial groups exposed to asbestos is of such magnitude that it precludes the identification of an independent etiologic role for cigarette smoking.

Hammond et al. have attempted to correct this methodological problem by comparing 12,051 asbestos insulation workers having complete smoking histories to a control population, with no smoking histories (42). Their control population consisted of 73,763 men from the American Cancer Society's prospective cancer prevention study who were similar to the asbestos workers in that they were white males; nonfarmers; had no more than a high school education; a history of occupational exposure to dust fumes, vapors, gases, chemicals, or radiation; and were alive as of January 1, 1967. Non-smoking asbestos workers showed a five times greater risk of dying from lung cancer than their smoking controls. Both smokers and nonsmokers exhibited a fivefold relative risk; however, the attributable risk was greater among the smokers. This higher attributable risk can be accounted for by the large

number of smokers in the asbestos-exposed population and the comparison population.

Liddell et al. has also studied the smoking patterns among asbestos workers through administering questionnaires to living workers or relatives of deceased workers, who died after 1951 (68). The authors report SMR's of 48 and 46 for nonsmokers and ex-smokers, increasing to 206 for heavy smokers. This study is unreliable however, because specific smoking death rates were not used for the calculation of expected lung cancer deaths, and this underestimated the risks among nonsmokers.

ARSENIC

Lung cancer was first observed to be excessive in a proportionate mortality study of workers exposed to sodium arsenic in the manufacture of sheep dip (45). Roth reported that 18 of the 47 autopsies done on German vinegrowers exposed to arsenical insecticides, died of lung cancer (111). Roth then compared lung cancer mortality rates of six rural and urban districts of the Moselle and one district of the Ahv (110). He found that the vineyard districts of the Moselle, using arsenical insecticides, had a higher proportionate mortality rate from lung cancer than did the urban and nonvineyard areas. The district of Ahv, however, had a lower incidence of lung cancer which Roth attributed to the non-use of arsenical insecticides. The autopsy results and the comparison of the vine-growing districts caused Roth to suggest an etiological link existed between arsenic insecticide exposure and an excess of lung cancer.

Pinto and Bennett studied 229 active copper smelter workers and pensioners (97). The pensioners were at least 65 years of age with 15 years or more of service in the plant. The authors concluded that there was no excess lung cancer in the smelter population. However, there was some indication that the nonexposed group had arsenic exposure because the urinary arsenic levels reported by Pinto et al. (98) and cited by Pinto and Bennett (97), indicated such exposure. Even though the overall cancer mortality rate was not statistically significant, the lung cancer mortality rate in the smelter group, 18 of 229 deaths or 7.9%, was greater when compared to the state as a whole, 518 of 13,759 (3.0%). Milham and Strong, in an examination of death certificates from the county where the smelter

was located, found 39 deaths due to lung cancer among county residents who had been employed at the smelter and 1 lung cancer death in an employee who was not a resident (90). Based upon the general United States population, the 40 deaths were statistically higher than the expected death rate of 18.

In another study of 8,047 white male U.S. copper smelter workers exposed to arsenic trioxide during 1938 to 1963, Lee and Fraumeni found that observed deaths ranged 6.0 times as high as expected when compared to their appropriate statewide population rates (63). The risk was also greater in those workers exposed to sulfur dioxide. In Japan, a case controlled study of 19 males who died of lung cancer, and of controls dying of other than lung, urinary, bladder, or skin cancer, Kuratsune et al. found that 11 of the lung cancer deaths occurred in men formerly employed at copper smelters—which was statistically in excess—compared to only 3 deaths in former copper smelter workers in the controlled group (60). Another study of 965 deaths, based on records at a Utah Copper Company, indicated that the smelter workers had the highest percentage of lung cancer deaths, 7.0% as compared to 2.2% among other employees or 2.7% when compared to the state as a whole (105). The authors concluded that both smoking and nonsmoking smelter workers experienced a higher frequency of lung cancer deaths than other workers in the company. The average duration of employment at the smelter was approximately 29 years. Although no in-plant arsenic measurements were taken prior to 1959, stack emissions for each year back to 1944 indicated levels three times those measured in 1959.

Baetjer et al. (9), Mabuchi et al. (76), and Ott et al. (94) also found excess lung cancer in workers handling arsenic in the manufacture of pesticides and herbicides. This information is important because, unlike the copper smelter, workers' contact with arsenic was not associated with additional exposure to other substances such as sulfur dioxide. Newman et al. indicate that in at least one study of copper mining and smelting communities, the predominate lung cancer cell type in persons exposed to arsenic was poorly differentiated epidermoid carcinoma; the second most common cell type was adenocarcinoma (93). Wicks et al. (148), however, suggests that the predominate cell type is in fact adenocar-

cinoma, a finding inconsistent with the hypothesis of Kreyberg (58) which states that small cell undifferentiated and epidermoid carcinomas are the only cell types that increase with exposure to inhaled carcinogens. Hood et al. (46) and Fern (33) were unable to demonstrate that arsenic was carcinogenic in the animal species they studied. Arsenic did, however, have teratogenic effects in this study.

BIS(CHLOROMETHYL)ETHER (BCME)

Alkylating agents have been used increasingly in industrial processes as intermediates in organic synthesis, organic solvents, bactericides, fumigicides, and cross-linking agents. During recent years, alkylating agents have come under intense scrutiny because of their mutagenic and tumorigenic activities.

One such alkylating agent is bis(chloromethyl)ether (BCME). It is also known as dichlorodimethyl ether and is frequently encountered as a contaminant of chloromethyl ether in concentrations up to 7%.

The carcinogenicity of BCME was first demonstrated in 1968 with skin painting in mice and subcutaneous injection in rats as the bioassay system. It was observed that of 20 mice treated with BCME, 13 developed papilloma, 12 of which progressed to squamous cell carcinoma. This was confirmed by additional experiments using subcutaneous injections of BCME in newborn mice (37).

Because industrial exposure to BCME is more likely to be respiratory than cutaneous, several animal inhalation experiments were undertaken. In 1971, Laskin et al. reported on 30 rats subjected to inhalation of BCME for 101 exposures at a concentration of approximately 0.1 ppm (61)(62). Five of the 19 rats autopsied revealed squamous cell carcinoma of the lung and five revealed esthesioneuropithelioma arising from the olfactory epithelium.

Epidemiologic Studies

Lemen et al. studied the sputum of workers exposed to BCME and compared it to above ground uranium miners since this group was known to experience no unusual lung cancer risk (65). At the time of sputum collection from the 115 workers, a questionnaire was completed to obtain information on the history of tobacco usage. Occupational histories were obtained on all current and past employees at the same time.

Because of the association between age,

tobacco usage, and degree of atypia in the sputa, it was deemed necessary to control for these confounding variables in evaluating the role of BCME in the etiology of lung cancer. Because the abnormal epithelium induced by cigarettes undergoes repair only after a substantial period of nonsmoking, an interval of five years or more of nonsmoking was defined as "former smoking." Cigar and pipe smoking was regarded as "nonsmoking" because their role in the etiology of lung cancer is very small, as compared to cigarette smoking.

BCME workers were matched sequentially with the use of a random list of surface miners based on similar cigarette usage (6 cigarettes/day, age at time of sputum collection, for five years).

Evaluation of cases and matched controls was undertaken separately for two groups: 1) male office employees and production and maintenance operation employees exposed less than five years; and 2) males employed for five or more years in the production and maintenance of anion-exchange resins.

The dichotomization was based on the observation that the prevalence of abnormal sputum rises with increasing years of exposure to a carcinogen, and on the theory that there is a latent period after exposure to a carcinogen before abnormal cells appear, although it appears to be shorter than the latent period before the induced carcinoma appears. This dichotomization was made after observation of the industrial hygiene survey was conducted at the facility.

Table VIII-1 shows the distribution of sputum cytology among those anion-exchange employees with the least or no exposure to BCME. So far, there is no association between type of work and degree of abnormal cytology (17% anion-exchange workers vs. 15% controls). Lemen et al. (65) also evaluated the incidence of lung cancer among BCME exposed workers.

By contrast, however, Table VIII-2 demonstrates the statistically significant association of abnormal cytology associated with exposure to BCME for five or more years. As listed in Table VIII-2, 34% of anion-exchange workers in this group had abnormal cytology, in contrast to only 11% for uranium surface miners.

Table VIII-3 shows that whereas only 0.54 cases of lung cancer would have been expected to occur in the plant population, five cases actu-

Table VIII-1**DISTRIBUTION OF SPUTUM CYTOLOGY**

Sputum Cytology: All Male Office Employees and Those Males Employed Less Than Five Years in the Production-Maintenance of Anion-Exchange Resins as Contrasted with Age-Cigarette-Matched Uranium Surface Employees

		Uranium Surface Employees		Total
		Normal, Metaplasia, Mild Atypia	Moderate to Marked Atypia	
Anion-Exchange Resin Employees	Normal, Metaplasia, Mild Atypia	49	10	59 (83%)
	Moderate to Marked Atypia	11	1	12 (17%)
	Total	60 (85%)	11 (15%)	71

* $\chi^{(2)}$ = Not significant.

Source: Lemen et al. (65)

Table VIII-2**RETROSPECTIVE COHORT INVESTIGATION OF LUNG CANCER INCIDENCE**

Sputum Cytology: Males Employed Five or More Years in the Production-Maintenance of Anion-Exchange Resins as Contrasted with Age-Cigarette-Matched Uranium Surface Employees

		Uranium Surface Employees		Total
		Normal, Metaplasia, Mild Atypia	Moderate to Marked Atypia	
Anion-Exchange Resin Employees	Normal, Metaplasia, Mild Atypia	13	2	15 (34%)
	Moderate to Marked Atypia	26	3	29 (66%)
	Total	39 (89%)	5 (11%)	44

* $\chi^{(2)}$ = Significant $p < .025$.

Source: Lemen et al. (65)

Table VIII-3

PRODUCTION AND MAINTENANCE WORKERS WITH FIVE YEARS EXPOSURE TO BIS(CHLOROMETHYL) ETHER IN AN ANION-EXCHANGE RESIN OPERATION*

Age	Person-Years	Expected	Observed
20-29	64	.01	0
30-39	198	.01	1
40-49	237	.09	2
50-59	106	.16	1
60-69	82	.23	1
70+	15	.05	0
Total	702	.55	5
SIR = $5 \times 100 = 924$		p < 0.01	
.54			

*Expectation based on respiratory cancer age specific incidence rates for white Connecticut males 1960-1962.

Source: Lemen et al. (65)

ally occurred, representing a significant excess ($p < 0.01$), and a ninefold increased lung cancer risk.

Pertinent data on these five cases are given in Table VIII-4. Since the exposure of all cases was intermittent over a period of time and the actual point of time when induction of the carcinomas occurred cannot be known, the period between first exposure and development of cancer is termed the induction-latency period.

DISCUSSION

The results of both the sputum cytology investigation and the lung cancer incidence study indicate that the workers of the plant studied by Lemen et al. have an unusually high cancer risk (65).

The distribution of sputum classes among production and maintenance workers with greater than five years' exposure is definitely different from the nonexposed group. The distribution of cytology findings in the nonexposed group is very similar to that in the control population. Since the controls do not differ significantly in other parameters such as age, sex, or cigarette smoking habits, it may be presumed that persons in the exposed group were exposed to a pulmonary irritant to which the controls and the in-plant contrast group were not. It is reasonable to attribute this risk to airborne BCME.

In the Lemen et al. study, three of nine recorded deaths were due to respiratory cancer, with four of nine recorded deaths due to malignancies (nodular histiocystic lymphoma and respiratory cancer) (65). This appears lower than

the number reported in 1973 by Thiess et al. (133) (Table VIII-5), who reported 8 of 14 deaths were due to respiratory cancer, and 12 of 14 deaths were due to all malignancies (cancer of bladder, testes, respiratory system, and stomach). Six of Thiess' reported cases occurred among 18 experimental technical department workers, a group known to experience very high exposures, as opposed to the group in the present study. When looking at only manufacturing workers, two lung cancer cases among 50 workers were reported by Thiess, a finding similar to the present study where 4 cases occurred among 136 manufacturing workers.

Examination of the data in Table VIII-6 indicated that the reported cases of bronchogenic cancer were among relatively young persons with a mean age of 47 years and that the induction-latency period had a mean of 15 years and is consistent with that of other reported cases of occupational lung cancer. The predominant histologic type of carcinoma found was small cell undifferentiated, and exposure ranged from 7 years, 7 months to 14 years with a mean of 10 years. The majority had smoked cigarettes. Considering that less than 40% of the person-years at risk of developing lung cancer among study cohort members occurred after 10 years since onset of employment, and indeed only 8% occurred after 15 years since onset of exposure, a vast majority of these workers have not yet developed sufficient latency for disease manifestation.

As shown in Table VIII-6, Figueroa et al. (34) reported that among 125 workers in a

Table VIII-4
BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	61	11yr, 3 mos	13	10/day-40 yr	large cell — undifferentiated
2	35	7 yr, 7 mos	8	unknown	small cell — undifferentiated
3	48	9 yr, 5 mos	10	40/day-25 yr	small cell — undifferentiated
4	40	12 yr, 10 mos	16	current smoker	small cell — undifferentiated
5	50	11 yr, 2 mos	26	heavy smoker	small cell — undifferentiated

Source: Lemen et al. (65)

Table VIII-5
BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	59	6	8	Smoking histories not given	Five of them were reported to have small cell undifferentiated carcinoma.
2	53	6	10		
3	31	8	8		
4	52	9	9		
5	65	6	15		
6	42	6	16		
7	58	6	16		
8	60	6	16		

Source: Thiess et al. (133)

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chemical plant participation in a program designed after the Philadelphia Pulmonary Neoplasm Research Project, (13) 4 cases of lung cancer occurred during the first 5-year period of observation. Considering that age, sex, and smoking habits were not significantly different, his observation of a 4.54% occurrence among the workers vs. only 0.57% among participants of the Philadelphia Pulmonary Neoplasm Research Project, is significant because it represents an eightfold excess. After further retrospective observation, 10 additional lung cancer cases

among individuals working in the plant were identified. No population figure or time period was given to determine the incidence.

Table VIII-7 shows that in 1973 Sakabe reported 5 cases of lung cancer among 32 employees exposed to BCME in a dyestuff factory in Japan (114). Four of the workers exposed were involved in the synthesis of onium dyestuff, but the fifth case was exposed only in the laboratory.

In the present study, as well as in the studies completed by Thiess et al. (133) and Figueroa

Table VIII-6
BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	37	7		none	unknown
2	33	8		20/days-20 yrs.	small cell— undifferentiated
3	39	8		20/days-20 yrs.	small cell— undifferentiated
4	47	10		20/days-0 yr.	small cell— undifferentiated
5	52	4		20/days-10 yrs.	small cell— undifferentiated
6	47	3		20/days-21 yrs.	small cell— undifferentiated
7	43	14		20/days-20 yrs.	small cell— undifferentiated
8	53	10		40/days-20 yrs.	small cell— undifferentiated
9	48	5		20/days-33 yrs.	small cell— undifferentiated
10	50	0-1		20/days-30 yrs.	epidermal
11	55	12		20/days-40 yrs.	small cell— undifferentiated
12	43	12		pipe only	small cell— undifferentiated
13	37	14		none	small cell— undifferentiated
14	44	12		none	small cell— undifferentiated

*Source: Figueroa et al. (34)

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et al., (34) the incidence of lung cancer among manufacturing workers, approximately 3 to 5%, were similar. This is contrasted with more than 12% found in Sakabe's study (114). His observation probably reflects the nature of the dye-stuff plant, where those at risk could be specifically identified. In the other studies it was extremely hard to determine those workers actually exposed to BCME: the entire production force had to be considered at risk, thus making the incidence conservative. In all four studies the ages, years of exposure, and induction-latency periods are not significantly different as tested

by an analysis of variance.

The predominance of small cell-undifferentiated or oat cell carcinomas noted in all four reports is noteworthy. A similar predominance of this histologic type has been noted for bronchogenic cancers associated with radon daughters (113) and with nitrogen mustard (150), a radiomimetic substance. Since the same histologic type is associated with BCME exposure and since there are similarities in the properties of BCME and nitrogen mustard, this predominance suggests that BCME may also be radiomimetic.

It is also noteworthy that most, but not all,

Table VIII-7
BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	47	9	14	moderate	unspecified
2	37	5	12	moderate	oat cell
3	41	9	13	moderate	unspecified
4	38	7	9	heavy	unspecified
5	45	4	13	moderate	adenocarcinoma

*Source: Sakabe. (114)

of the men who developed lung cancer had smoked cigarettes. This suggests that cigarette smoking may interact with the primary carcinogen in a promotional or synergistic fashion just as it does with asbestos (120) and radiation cancers (4). The fact that some nonsmokers are in the group and that the lung cancers occur at much younger ages and are of a different cell type than normally found with cigarette-induced lung cancers, provides further evidence that BCME is the primary agent, rather than cigarette smoke.

COKE OVENS

The long delay between the first observation of human cancers induced by the combustion products of bituminous coal and the development of evidence describing the cancer risks among men employed at coke plants in the steel industry has covered a period of two hundred years.

In 1962, the United States Public Health Service, in collaboration with the Department of Biostatistics, University of Pittsburgh School of Public Health and three major steel firms, initiated a study to analyze the mortality experience of men employed in the steel industry in 1953. The purpose of this study was to determine whether particular patterns of mortality among workers employed at certain trades or at certain work processes might provide leads to causative agents for occupational diseases. The methodological approaches to this study and many of the findings have been presented in a series of papers published in the *Journal of Occupational Medicine* (52)(108).

Using detailed work histories, going back to original employment with the steel firms, it was possible to determine cause-specific rates of

mortality for more than 60 work areas within the industry and for a great variety of trades. As shown in Table VIII-8, unusual patterns of site specific cancer have been noted for several work areas. Because of the unusually high lung cancer risk observed among coke plant workers and the variety of cancer sites in excess for men employed in this area, more detailed analysis of this experience was undertaken. As seen in Table VIII-9, the greatest risk is noted for those with the longest exposure and those employed where exposure to emissions is greatest on the topside. The United States Department of Labor has now proposed a standard to protect workers from these emissions. The detailed evidence indicating the high risk of specific cancers among men employed at the coke plant, and the demonstration of a relationship between the level of disease response, was crucial in reaching this decision.

As noted previously, the initial evidence suggesting that carcinogenic agents are produced during the carbonization or combustion of bituminous coal was presented by Percivall Pott in 1775. Since that time, a great amount of information indicating excess cancer of several sites among workers in other coal combustion or carbonization occupations has been noted and, in fact, a report of official statistics from England and Wales for the years 1921 to 1938 showed an excess lung cancer mortality for gas producemen, chimney sweeps, and several categories of gas works employees (52). The excess indicated for gas stokers and coke oven chargers was approximately threefold.

ALUMINUM

In trying to assess the extent of the lung cancer problem in the aluminum industry, a similar situation as seen for gas workers and coke oven

Table VIII-8

OBSERVED AND EXPECTED CANCER AND RELATIVE RISKS BY CANCER SITES FOR WORKERS EMPLOYED FIVE OR MORE YEARS IN SPECIFIED WORK AREAS ALLEGHENY COUNTY STEELWORKERS, 1953 - 1966

Site	I.C.D List Numbers	Work Area	Obs.	Exp.	Relative Risk
All Cancers	140-205	Coke Plant	119	91.9	1.51**
Digestive Organs	150-159	Stainless Annealing	6	2.3	2.80*
Esophagus	150	Open Hearth	13	6.6	2.41*
Stomach	151	Blast Furnace	17	12.3	1.45
Large Intestine	153	Coke Plant	12	7.8	1.77
Rectum	154	Machine Shop	6	2.5	2.55
Respiratory System	160-164	Coke Plant	45	24.9	1.81**
		Mason Department	17	11.0	1.57
		Blacksmith Shop	8	3.8	2.16
		Machine Shop	24	16.6	1.48
Genito-Urinary Organs	177-181	Coke Plant	17	10.4	2.01*
Prostate	177	Janitors	7	3.4	2.28
Kidney	180	Janitors	6	2.3	3.11*
Leukemia & Lymphoma	200-205	Coke Plant	6	1.5	15.20**
		Heat Treating & Forging	5	2.2	2.87

*Significant at 5% level.

**Significant at 1% level.

Source: Redmond (100)

workers thirty years ago, is observed. That is, a review of death certificates shows that persons employed in the industry are at a high risk of developing cancer. Furthermore, men employed in certain work areas with exposures related to those found at the coke plant appear to be at the greatest risk.

During the electrolytic reduction of alumina to aluminum a variety of toxic substances are released which may contaminate the workroom air. Among these substances are: hydrogen fluoride, fluoride fume, dust, and carbon monoxide which are potential contaminants whose biological effects are recognized. In addition, coal-tar-pitch volatiles are also released in the process, either in the anode preparation area for pre-baked anodes, or in the pot lines where Soderberg self-baking cells are used.

Investigators from the Soviet Union have reported a significantly higher mortality for all cancers and for specific sites such as lung, bronchi and pleura, and have reported an increased incidence of skin cancer among workers in the aluminum "electrolyzer shops" in comparison with the general population in the same cities

(57)(69). Unfortunately, neither of these studies is sufficiently documented to allow firm conclusions.

Milham has reported an increase in proportionate mortality from total cancer, cancer of the pancreas, respiratory system, and malignant lymphomas among aluminum workers in Washington State (Table VIII-9) (89).

The National Institute for Occupational Safety and Health (NIOSH) has conducted environmental surveys of aluminum reduction facilities in the East and Northwest United States, monitoring for coal tar pitch volatiles and a variety of other potentially hazardous substances (125). These surveys included reduction plants using pre-baked anodes, the vertical pin Soderberg anodes, and horizontal pin Soderberg anodes. The findings indicate that the concentration of coal-tar-pitch volatiles (CTPV), as measured by the benzene soluble fraction technique, were almost all elevated above the current OSHA Standard of 0.2 mg/M CTPV for an 8 hour time-weighted-average. The levels were highest in the Soderberg potrooms, presumably because the pitch is heated and "baked off" the

Table VIII-9
PROPORTIONATE MORTALITY RATIOS (PMR's)
WHITE MALE DEATHS IN WASHINGTON STATE, 1950-1971

Aluminum Workers				
<i>Cause of Death</i>	<i>I.C.D. Number*</i>	<i>Deaths</i>		
		<i>Obs.</i>	<i>Exp.</i>	<i>PMR</i>
All Malignant Neoplasms	140 - 204	129	103	126**
Cancer of Esophagus	150	5	2	232
Cancer of Pancreas	157	13	6	204**
Cancer of Respiratory System	160 - 165	40	31	128
Cancer of Testis	178	3	1	251
Cancer of Brain	193	6	4	155
Malignant Lymphoma	200 - 202	10	4	250**
Hodgkin's Disease	201	4	2	164

*I.C.D. = International Classification of Diseases, 7th Revision.

** $p \leq .05$

Source: Milham (89)

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anode in these potrooms. In contrast, the lowest measurements were in the potrooms using pre-baked anodes. This type of carbon anode already has the pitch "baked off" before being used in the reduction area.

In a 1976 study of chronic respiratory disease among aluminum reduction workers, sputum cytology was utilized to determine the degree of abnormal cells in the respiratory tract as an early indication of cancer (24). Because of certain limitations of that study, the authors were unwilling to draw any conclusions regarding the carcinogenic risks among the study group as compared to matched controls. However, review of the results from that study leads us to conclude that the evidence of potential carcinogenic risk for potroom workers is certainly quite consistent with the previously mentioned mortality observations. When consideration is given to the sputum cytology classification of moderate atypia or higher, a significant ($p < 0.01$) difference is observed between the study group (30/390) and the control group (5/195). Moreover, when consideration is restricted to causes of suspicious and positive cancer, there are 6/390 meeting such criteria in the study group, compared to 0/193 in the control group. It also should be noted that the control group in this study had a greater exposure to known carcinogens, according to prior work history, so that difference in cancer risks are underestimated. Other studies on workers ex-

posed to recognized pulmonary carcinogens have used sputum cytology and demonstrated its validity as an early indicator of cancer (35)(65).

CHROMIUM

In 1946, an early association of lung cancer with exposure to chromium was made by Alwens and Jonas, when they noted an excessive frequency in workers involved with the heavy chemical industry in two German towns (2). It was concluded that the causal agent was chromate dust. These observations were followed by Machle and Gregorius in the United States where a study of 6 chromate plants revealed 32 cases of cancer of the bronchus and lung an estimated relative risk of 25% (77). Looking at 290 lung cancer patients from two hospitals near a chromate-producing plant, Bactjer found that 3.8% were chromate workers, a rate significantly higher than among a random sample of other hospital admissions (8). Mancuso, looking at a chromate-producing plant in Ohio, found a ratio of lung cancer deaths to all deaths of chromate workers approximately 15 times greater than that of the general population of the same county (78). In another study of chromate workers over an 11-year period, based upon deaths reported for those enrolled in sick benefit associations, Brinton et al. reported 29 times as many respiratory cancer deaths as would have been expected from the general population (15). A United States

Public Health Service survey by Gafafar of death claims submitted to the sick-benefit plans of seven U.S. chromium manufacturing plants, found for white employees an excess of 10 lung cancer deaths observed as compared to 0.7 expected (SMR = 1429) (36). Black employees had 16 observed lung cancer deaths as compared to 0.2 expected (SMR = 8000). In the cross-sectional medical portion of this study, 897 workers were examined and 10 were found to have bronchogenic carcinoma. When compared to another cross-sectional x-ray survey in Boston, the 10 cases of bronchogenic carcinoma among chromium workers accounted for a prevalence rate of 115 per 100,000 compared to that in the Boston survey of 20.8 per 100,000.

Continued evidence has accumulated from epidemiologic studies in the chromate-producing industries around the world as can be seen in Table VIII-10. Work has also continued to look at various other types of exposure to chromium in the pigment industry, plating industry, ferrochromium industry and other industries where exposure to chromium compounds occur and are summarized in Tables VIII-11, VIII-12, VIII-13, VIII-14.

In conclusion, the data are sufficient proof that respiratory carcinogenicity does occur in excess in men exposed during chromate production, and suggestive of excesses during other exposures to chromium or its compounds. The data from rat studies tend to incriminate chromium as the causative agents (47). The data appear inadequate at the present time to evaluate the carcinogenic potential of the other chromium compounds.

NICKEL

In 1932, the first human evidence of an association of nasal cancer among workers exposed to nickel was described in the report of the Chief Inspector of Factories (18). In this report, 10 cases of nasal cancer were described in refinery workers in Wales. Further follow-up from this same refinery in 1950 reported 52 cases of nasal cancer and 93 cases of lung cancer (19). In 1970, Doll et al. studied 845 men employed in the same refinery who had been employed 5 years or more and had been hired prior to 1971 (28). In men hired prior to 1925, deaths from lung cancer were 5 to 10 times higher than expected when compared to overall British Mor-

tality rates. The deaths from nasal cancers were 100 to 900 times of that which was expected. This was in comparison to men employed after 1925, who showed no signs of excess from these cancers. These results suggest that the carcinogenic hazard in the refinery had been removed by 1925 (26)(91). Doll, et al. observed that by 1970 nasal cancer still persisted essentially unchanged even after the carcinogen was eliminated whereas the lung cancer incidence had decreased over a period of time (28).

Nasal cancer excesses have also been reported in nickel refineries in Canada (20)(82) (137), in Norway (73) (95), the German Democratic Republic (55)(56)(109), Japan (135), in the USSR (115)(116)(131)(132)(151), and in New Caledonia (67).

Kreyberg (59) further evaluated the lung cancer deaths, including those reported by Loken (73) and Pederson et al. (95), with specific emphasis on tobacco consumption, occupation, and cell type. He confirmed that Nickel refinery workers experienced an excess of lung cancer when compared to a reference population not so exposed. In addition, he showed that the majority of lung cancers were of the small cell anaplastic carcinoma and epidermoid carcinoma cell types and that the victims had a history of tobacco consumption. Kreyberg concluded that nickel induced lung cancer is higher than the risk found in the general population, but that the true risk of nickel exposure alone will not be known until a suitably large number of nonsmokers exposed to nickel can be studied. He did not attempt to estimate the magnitude of the synergism, if any, between tobacco and nickel in inducing lung cancer.

Doll et al. indicate that the exact nature of the carcinogenic agents in nickel refineries are not known and that the cancer risk is associated mostly with the earlier stages of nickel refining (28). Some suggestions are that respirable particles of nickel subsulphide and nickel oxide are most suspect (20).

Recently, Costa and Mollenhouer have demonstrated that particles $\leq 5 \mu\text{m}$ of crystalline nickel subsulfide were actively phagocytized by cultures of Syrian hamster embryo cells and Chinese hamster ovary cells (22). While cells did not take up significant quantities of similar sized particles of amorphous nickel monosulfide, this does suggest that carcinogenic activity is associ-

ated with cellular uptake. Animal studies support inhaled nickel subsulfide has produced lung cancer in rats. Inhalation exposure in rats to nickel carbonyl was also associated with several pulmonary malignancies (49). Three case reports of lung cancer occurred in workers during nickel plating and grinding operations (14)(130)(134).

BERYLLIUM

It has been shown that beryllium is carcinogenic in many animal species (48). Mancuso, in a study of 1,222 white male beryllium production workers employed between 1942 to 1948 in Ohio and Pennsylvania, found an excess of lung cancer when compared to the United States white male population (80). In Ohio, 25 lung cancers were observed as compared to 12.52 expected for a statistically significant excess, and in Pennsylvania, even though not statistically significant, there was an excess of lung cancer (40 cases observed vs. 29.11 expected) when followed through 1977. In 1980, Mancuso compared the mortality experience in a beryllium cohort of 3,685 white males employed between 1937 and 1948 and followed through 1976 with viscose rayon workers and found a statistically significant excess of lung cancer (80 observed vs. 57.06 expected) (79).

According to the Beryllium Case Registry, 421 white males suffering from berylliosis between 1952 and 1975 had excess cases of lung cancer (7 vs. 3.3 expected based upon the United States white male rates) (50). Wagoner et al., in a retrospective cohort study of 3,055 white male workers employed between 1942 and 1948 and followed from 1968 through 1975 in the beryllium refining industry, found an overall statistically significant excess rate at the $p < 0.05$ level for lung cancer (47 observed vs. 34.29 expected, based on U.S. white male rates)(142). When looking only at white male workers with 25 years or more after initial exposure, Wagoner et al. found 20 observed and only 10.79 expected ($p < 0.01$).

MUSTARD GAS

Respiratory tract cancer has been observed in workers manufacturing mustard gas. Wada et al. determined that 33 deaths from respiratory tract carcinoma had occurred in mustard factory workers since 1952 (138). The 30 historically confirmed neoplasms appeared centrally rather than peripherally and were squamous or undifferentiated in cell type. These findings tend to

strengthen the inconclusive results obtained in the 1914-1918 study which show that mustard gas may have been responsible for the lung cancer deaths among those soldiers exposed (10)(17).

FLUORSPAR

Fluorspar, the mineral calcium fluoride, is mined commercially in various parts of the world. However, the only study of health effects associated with miners on fluorspar was that done by de Villiers and Windish in Newfoundland (23). Their results show that, since 1952, two or three deaths from primary lung cancer have occurred each year among males living in a small fluorspar mining community. After comparison of these deaths with a control community of similar size in the same geographical region and with the population of the rest of Newfoundland, the observed death rate from lung cancer was about 29 times more than expected. This confirms the probability of an associated occupational factor. The most likely associated etiological factor was the finding of radon daughter products in concentrations similar to those found in uranium mines. It is of interest that no radioactive ore bodies have been found in the mine.

RADON DAUGHTERS

As early as 1557, fatal lung disease was occurring in miners of uranium-bearing ore in the Erz Mountains of Europe (1). In 1879, this lung disease was later identified as malignant neoplasia (lymphosarcoma) by Harting and Heese (44). By 1913, the miners from the Schneeberg mines were found to be dying of lung cancer at a rate of 40 percent of all deaths (6). In Czechoslovakia, 9 of 17 deaths were observed between 1929-1930, among miners of uranium-bearing ores, which were due to lung cancer (99). Further study by Peller in 1939 indicated that the rate of lung cancer among miners of uranium-bearing ores in the Czechoslovakia mine was 9.77 per 1,000 which was much higher than that reported among nonmining males living in Vienna, Austria (0.34 per 1,000) (96).

In 1950, the Public Health Service began looking at hazards to U.S. uranium miners in 1950. Between 1954 and 1960, 5,370 miners and millers submitted to pulmonary function and chest radiography tests as part of complete physical examinations. Demographic, social and past occupational history data was also collected. In

1964 Wagoner et al. demonstrated that the mean cumulative radiation exposure of the U.S. uranium miners with respiratory cancer was significantly greater than miners with nonrespiratory disease (139). In addition, Wagoner et al. demonstrated a statistically significant excess of respiratory cancer among underground uranium miners which could not be attributed to age, cigarette smoking, heredity, self-selection, diagnostic accuracy, prior hard-rock mining or nonradioactive ore constituents, including silica dust. In another study by Wagoner et al., it was demonstrated that a statistically significant excess of lung cancer did occur in an exposure-response relationship with airborne radiation even after cigarette smoking was excluded as a confounding factor (141). Lundin et al., using data gathered during the U.S. Public Health Service study projected that exposure at 4 working level months (WLM) per year for 30 years could be expected to double the respiratory cancer risk over a 40 year period (74). Epidermoid, small cell undifferentiated, and adenomatous histologic types were all increased among uranium miners, with the small cell undifferentiated type showing the greatest increase (5). With relation to cigarette smoking, in 1976, Lundin et al. hypothesized that if the latent period of radiogenic lung cancer were longer in nonsmokers as compared to smokers (due to the predominance of promoting agent in cigarette smoke) then it is probably too early to expect lung cancers among the nonsmoking uranium miners (74). Both Wagoner et al. (140) and Archer et al. (3) tested the Lundin et al. hypothesis and found that nonsmoking or Indian uranium miners smoking lightly had a mean latent period of 19.1 years as contrasted with 13.7 years for a group of heavy smoking white uranium miners dying of lung cancer. Recently Gottlieb and Husen reported that, among 17 lung cancer cases in Indians diagnosed during 1965 through 1979, 14 were nonsmokers and that 10 had small cell undifferentiated histology as previously shown to be predominant among white underground uranium miners in the United States (39).

Reports from Canada (40); Czechoslovakia (122)(123)(124) and Sweden (7)(51)(104)(126)(127) each have shown an excess of lung cancer associated with radon daughters exposures.

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Table VIII-10
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PRODUCING INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
Six chromate plants ^a ; -active employees; -4-17 years before 1948; 156 deaths	Cancer mortality in oil-refining company, 1933-1938	Bronchus and lung	32	25	Digestive	13	2	0.01-21.0 mg/m ³ (total Cr)	Machle & Gregorius (1948)
Case-control; lung cancer; 290 cases near US chromium plant	Random sample of hospital admissions	Lung	11 ^b	*				Levels determined in 1947: 25-6865 µg/m ³	Baetjer (1950b)
Cohort study; US chromate-producing plant; workers employed 1 or more years 1931-1949; 33 deaths	Proportionate mortality for county		6	15 ^c					Mancuso & Hueper (1951)
Seven US chromium plants; active employees 1940-1950; 5522 person-years	US males white black	Lung	10 16	14.3* 80.0	Other sites	6	1NS		Gafafer (1953)
Health survey 897 workers	Boston X-ray survey		10	53 (prevalence ratio)					
Three UK factories; 723 men employed 1949-1955	Cancer mortality England and Wales, 1951-1953	Lung	12	3.6*	All other sites	no excess			Bidstrup & Case (1956)

Table VIII-10

EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PRODUCING INDUSTRIES (Continued)

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
Three US chromate-producing plants; 1212 males employed 3 or more months between 1937-1940; status to 1960	Cancer mortality US males, 1950, 1953, 1958		71	8.5*	All other sites	32	1.3		Taylor (1966)
Same populations as Taylor (1966); 1941-1960	Cancer mortality US males, 1950, 1953, 1958		69 (2 maxillary sinus)	9.4*	Digestive system	16	1.5NS		Enterline (1974)
Same plant as Mancuso & Hueper (1951); employed 1 or more years 1931-1937; all jobs related to exposure to total and soluble/insoluble chromium; lifetime exposure in months calculated	No independent comparison group	Lung	41	Crude Hoyeau rate: 369.7/100,000				[Tables show increased lung cancer risk with increasing total Cr when insoluble level constant and suggest increasing lung cancer with increasing soluble Cr when total constant; exposure into solubility categories may be questioned]	Mancuso (1975)
Same US plant as Bactjer (1959b);	Baltimore City mortality	Lung (162)	59	2*				New sites with better controls;	Hayes <i>et al.</i> (1979)

Table VIII-10
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PRODUCING INDUSTRIES (Continued)

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
2101 workers employed 3 or more months 1945-1974; status 1977 (88% complete). Populations working in new and/or old production sites		Cohort 1940-1949	13	3*				2-17 $\mu\text{g}/\text{m}^3$ Cr in 1973-1975. Significant excess of lung cancer for workers in 'special products' and dichromates (soluble Cr[VI]); case-control	
		Cohort 1950-1959							
		<3 years' work:							
		new	2	0.7					
		old	12	1.8NS					
		>3 years' work:							
	new	3	4NS						
	old	9	3.4*						

*One plant, with 37 deaths and 10 respiratory cancers but with no adequate employment records available, has been excluded.

^bOnly 11 cases had been exposed to chromium compounds *versus* none in controls.

^cSignificant if χ^2 is applied, but the small number of cancers due to chromate makes use of this procedure questionable.

*—significant

NS—not significant

Others not known or not tested.

Source: IARC (48)

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Table VIII-11
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PIGMENT INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers			Other Cancers		Notes	References
		Site	No.	Estimated Relative Risk	Site	No.		
Norwegian pigment production since 1948; 24 males with over 3 years' employment to 1972	Cancer Registry of Norway	Lung	3	38*	Gastro-intestinal	1	Exposures to Cr in mg/m ³ : current, 0.01-1.35; estimated lifetime, 0.5-1.5. Materials; PbCrO ₄ , ZnCrO ₄ , Na ₂ Cr ₂ O ₇	Langard & Norseth (1975)
UK chromate pigment factories: A, lead & zinc chromate; B, lead & zinc chromate; C, lead chromate; followed to 1977	UK mortality rates	Lung High & medium exposure					Lung cancer occurred with latency (25 years); excess disappeared after 25 years	Davies (1978, 1979)
		A(1932-54), 175 workers	18	2.2*				
		B(1948-67), 116 workers	7	5.0*				
		A(1932-54), 175 workers	2	1				
		C(1946-67), all exposures	2	0.7				

*—significant

NS—not significant

Others not known or not tested.

Source: IARC (48)

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Table VIII-12
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PLATING INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
UK chromium plating workers since 1946	Not stated	Lung	49	1.4*				Incomplete information	Waterhouse (1975)
54 UK chromium plating plants; 1056 male platers; 1099 male controls	Nonexposed workers in plants and in 2 non-plating industries		24	1.8NS	Total Cancer	44	2.0*	Current exposure to 0.01 mg/m ³ chromium trioxide. Exposure to several metals including Ni.	Royle (1975a,b)
					Gastro-intestinal	8	2.0NS		
					Other Sites	12	2.4NS		
Japanese chromium plating industry; 952 workers with >6 months' exposure	4236 nonexposed workers from same industry		0	<1	Total cancer	5	<1	The very low relative risks suggest incomplete follow-up.	Okeubo & Tsuchiya (1977)

*—significant

NS—not significant

Others not known or not tested.

Source: IARC (48)

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Table VIII-13
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN FERROCHROMIUM INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
Soviet workers in 1955-1969 in the ferrochromium alloy industry	City mortality	Lung	not given	(males) 4.4-6.6* by age	Total Cancer Oesophageal	not given not given	(males) 0.5-3.3* 2.0* 11.3*	Exposed to Cr[III], Cr[VI] and benzo [a] pyrene; highest risk with dust exposure; no numbers provided	Pokrovskaya & Shabynina (1973)
Swedish ferrochromium plant; ferroalloys; 1876 workers for 1 year or more 1930-1975; traced by parish lists and cancer registry; 380 deaths	Classification of work areas by exposure to Cr[III] and Cr[VI]; comparison with county or national statistics	Mortality study of all workers	5	1	Prostate (all workers)	23	1.2NS	Asbestos exposure	Axelsson et al. (1980)
		Maintenance workers	4 (2 mesotheliomas)	4.0*					
Norwegian; ferrochromium and ferro silicon; 976 workers employed 1928-1960	General population; internal comparison with nonexposed	Lung (ferrochromium workers)	7	A ^a 2.3NS B ^b 8.5*	Stomach (ferrochromium workers)	5	1.5NS		Langard et al. (1980)
					Prostate (all workers)	20	1.5NS		

*— significant

NS—not significant

Others not known or not tested.

^aOn the basis of national rates.

^bOn the basis of an internal reference population.

Source: IARC (48)

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Table VIII-14
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS
IN OTHER INDUSTRIES WITH EXPOSURE TO CHROMIUM COMPOUNDS

Study Population	Comparison Population	Respiratory Cancers		Other Cancers		Notes	References		
		Site	No.	Estimated Relative Risk	Site			No.	Estimated Relative Risk
Chemical manufacture; 30,000 employees; cases 1958-1970	Nonexposed workers; used crude incidence		not given		All malignant neoplasms for chromate factory ^a	852/ 10,000	10.1	Exposure to chromium trioxide, iron oxide, nitric acid	Bittersohl (1971)

^aNumbers calculated by National Institute for Occupational Safety and Health (1975) from a histogram. This study was done in a big chemical manufacture industry, and the numbers of total malignant neoplasms associated with exposure to different compounds are given.

Source: IARC (48)

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PATHOLOGY OF OCCUPATIONAL LUNG CANCER

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Val Vallyathan

The association of environmental factors with lung cancer is well recognized. Among these factors cigarette smoking, air pollution, and occupational exposures to specific industrial agents such as asbestos, arsenic, uranium, chromium, nickel, and chloromethyl ether are considered paramount. Unfortunately for epidemiological purposes, the majority of industrial workers smoke and many live in polluted urban environments; thus separation of risk factors is difficult. The issue is complicated further by synergistic and additive effects between risk factors. Two examples of the former are seen with cigarette smoke and asbestos (35) and cigarette smoke and uranium (6).

The overwhelming majority of lung cancers occur in smokers, and in the United States squamous cell carcinoma is known to be the most prevalent histological type of tumor in males (13)(23)(46) followed by adenocarcinoma, oat cell carcinoma, and large cell carcinoma, respectively (49). The existence of four major histological types of lung cancer is useful as it can be evaluated by pathologists to study the possible influence of smoking, occupational, and other factors on the histogenesis of pulmonary neoplasms. In addition to histological type, the lobe of origin and its position within the lobe (central or peripheral) may also be important.

The majority of studies reporting the distribution of lung cancer by histological type have used the WHO histological classification of lung tumors (24) and its revisions (41)(53).

Histologically, lung cancers can be divided into four major categories: *squamous cell carcinoma*, *small cell carcinoma*, *adenocarcinoma*, and *large cell carcinoma*. From the clinical standpoint separation into distinct types is important in view of their different natural histories (28) and responsiveness to therapy (12). These four types together account for approximately 85%

of all primary malignant neoplasms of the lung. Lung cancer can be further subdivided into subtypes based on distinct morphological characteristics (53). Subtypes and degree of differentiation may also be important in relation to occupational exposures (29). Other primary malignant tumors of the lung include mixed combined tumors showing features of two or more major types, bronchial gland tumors, carcinoid tumors, carcino-sarcomas, sarcomas, and other rare tumors (Table VIII-15). An association between benign lung tumors and occupational exposure has not been demonstrated; therefore, these will not be considered further. The relationship between malignant tumors of the pleura (mesotheliomas) and occupation are addressed elsewhere.

Grossly, lung cancers may be classified as hilar types (presumed origin within a bronchial wall) or peripheral types (presumed origin in small airways or pulmonary parenchyma).

The majority of *squamous cell carcinomas* are of the hilar type, arising from the major to segmental bronchi. Multicentric origin is also common. These are thought to originate in areas of metaplasia or dysplasia, though this is not always the case (42). Squamous cancers can be further subdivided into: 1) polypoid type, 2) nodular infiltrating type, 3) superficial infiltrating type, and 4) combinations of 1, 2, and 3 (37). The tumors are usually large, pale yellow in color and may show areas of central necrosis. Histologically, the tumors are classified into well, moderately, or poorly differentiated depending on the degree to which they exhibit keratinization and/or intercellular bridges. Hypercalcemia is the most important paraneoplastic syndrome of squamous cell tumors (37).

Small cell carcinomas arise in both major bronchi and in the lung periphery. They typically spread beneath the mucosa to produce raised

Table VIII-15
HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS

I. Epithelial Tumors

- A. Benign
 - 1. Papillomas
 - a. Squamous cell papilloma
 - b. "Transitional" papilloma
 - 2. Adenomas
 - a. Pleomorphic adenoma ("mixed" tumor)
 - b. Monomorphic adenoma
 - c. Others
- B. Dysplasia, Carcinoma *In Situ*
- C. Malignant
 - 1. Squamous cell carcinoma (epidermoid carcinoma)
Variant:
 - a. Spindle cell (squamous) carcinoma
 - 2. Small cell carcinoma
 - a. Oat cell carcinoma
 - b. Intermediate cell type
 - c. Combined oat cell carcinoma
 - 3. Adenocarcinoma
 - a. Acinar adenocarcinoma
 - b. Papillary adenocarcinoma
 - c. Bronchiolo-alveolar carcinoma
 - d. Solid carcinoma with mucus formation
 - 4. Large cell carcinoma
Variants:
 - a. Giant cell carcinoma
 - b. Clear cell carcinoma
 - 5. Adenosquamous carcinoma
 - 6. Carcinoid tumour
 - 7. Bronchial gland carcinomas
 - a. Adenoid cystic carcinoma
 - b. Mucoepidermoid carcinoma
 - c. Others
 - 8. Others

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Table VIII-15
HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS (Continued)

II. Soft Tissue Tumors
III. Mesothelial Tumors
<hr/>
A. Benign mesothelioma
B. Malignant mesothelioma
1. Epithelial
2. Fibrous (spindle-cell)
3. Biphasic
IV. Miscellaneous Tumors
A. Benign
B. Malignant
1. Carcinosarcoma
2. Pulmonary blastoma
3. Malignant melanoma
4. Malignant lymphomas
5. Others
V. Secondary Tumors
VI. Unclassified Tumors
VII. Tumor-like Lesions
A. Hamartoma
B. Lymphoproliferative Lesions
C. Tumorlet
D. Eosinophilic granuloma
E. "Sclerosing haemangioma"
F. Inflammatory pseudotumor
G. Others

Source: (53)

longitudinal folds (37). The primary tumor may be exceedingly small and the first clinical indication may result from entrathoracic metastases. Necrosis is less frequently seen in small cell carcinomas than in squamous cell carcinomas and cavity formation is rare. Microscopically, the tumors may be divided into oat cell, intermediate cell and combined oat cell carcinoma (53). The oat cell type is characterized by small cells with round or oval hyperchromatic granular nuclei, ill defined borders, and scanty cytoplasm. The cells tend to form trabeculae and rosettes. The intermediate cell type is similar to the oat cell

type but has more abundant cytoplasm and distinct cell borders. The combined type is composed of areas of definite oat cell carcinoma with adjacent areas of either squamous cell carcinoma and/or adenocarcinoma. At the ultrastructural level small cell carcinomas can be distinguished from the other types of carcinoma by the presence of dense neurosecretory type granules with limiting membranes. Small cell carcinomas frequently produce polypeptide and biogenic amine hormones which give rise to a number of clinically important syndromes (21).

Adenocarcinomas may arise in the hilar or

peripheral regions of the lung; the majority arise in the latter location. The peripheral type is thought to arise from cells lying distal to the terminal bronchioles. Well differentiated tumors tend to have poorly defined borders whereas the poorly differentiated tumors may secrete copious mucus which may grossly resemble *Klebsiella pneumonia* (28). Their occurrence in fibrotic lung disease has led to speculation that these tumors arise in areas of cubodial metaplasia adjacent to scars. This theory is difficult to prove, however, as adenocarcinomas may provoke a marked desmoplastic fibrous stromal response. Minute, presumably early, adenocarcinomas have also been demonstrated in areas devoid of fibrosis (37)(38). Because the most common type of metastatic carcinoma to the lungs is adenocarcinoma, it is important to exclude other possible primary sites of origin before a definitive diagnosis is made. Inclusion of metastatic tumors would tend to increase the frequency of adenocarcinomas. Although it is rare, adenocarcinomas can secrete a salivary gland type amylase (1). Histologically, they may be grouped into acinar, papillary, bronchiolo-alveolar, and solid carcinomas with mucus formation. The first two are further classified into well, moderately, and poorly differentiated adenocarcinoma.

Large cell carcinomas are composed of undifferentiated malignant cells showing no features of the other histological types. They are thus diagnosed by exclusion. Included in this category are tumors showing clear cells or giant cells. On the basis of electron microscopical studies the majority of these tumors probably represent poorly differentiated squamous or adenocarcinomas (37). The frequency distribution of histologic types is probably related to the size of the biopsy available for study. The larger the sample the greater the chance of the tumor showing areas of squamous or adeno differentiation. Large cell carcinomas tend to arise from more distal bronchi, have well defined rounded borders, and show hemorrhage and necrosis on cut section. An inflammatory cellular reaction is frequently seen with the giant cell type. Human gonadotrophic hormone production has been described in association with the large cell variant (17).

Several studies have reported the relative frequencies of the different histological types of lung cancer in the general population and these have largely formed the basis for comparison

with occupational groups. Determining the true prevalence of the different histologic types in occupational cohorts has proven difficult due to numerous confounding variables. Some of these will be considered briefly. First, in most studies the occupational histories of the comparison population are not known or are incomplete, thus biases due to occupation may remain undetected. Second, as mentioned earlier, the vast majority of lung cancer cases occur in smokers, thus occupational effects on lung cancer histogenesis are superimposed on the already existing effects of smoking. In many studies smoking histories are incomplete and in most, cumulative exposures are not known. Both of these factors influence cell type frequencies. All types of lung tumor show a dose-response relationship with cigarette smoking. Several studies indicate that this effect is greatest for squamous cell carcinomas (8)(25)(47); other studies indicate oat cell tumors are more responsive (4)(55). Third, it has been shown that the frequency distribution of histological type is dependent on the method of diagnosis. For example, centrally located tumors, which tend to be squamous cell carcinomas, are more easily accessible to bronchoscopy, whereas peripheral tumors, which tend to be adenocarcinomas, are more likely to be diagnosed at autopsy (19). Thus studies based on autopsy material will differ from biopsy based studies. Fourth, the frequency distribution of lung cancer by cell type appears to be changing. In particular, there is evidence that the proportion of adenocarcinomas and possibly squamous cell carcinomas in the general population is increasing (5)(45). While part of this trend may reflect changes in diagnostic criteria, there is also evidence that this is a real phenomena. Fifth, there is considerable inter and intra observer variability in tumor classification by pathologists, particularly for the less well differentiated types (16). Sixth, age at diagnosis appears to influence the frequency distribution of different histological types (48), with a greater proportion of squamous cell carcinomas appearing in the older groups. Finally, there are distinct sex differences with relatively more adenocarcinomas in women (7).

Studies showing the distribution of lung cancer by histological type in the general population categorized by sex and smoking status are summarized in Tables VIII-16-VIII-22. These indicate that in male cigarette smokers (Table VIII-16), the predominant cell type is squamous

with lesser frequencies of adenocarcinoma, small cell undifferentiated carcinoma, and large cell undifferentiated tumors in that order. In female smokers adenocarcinomas predominate (Table VIII-17).

Very few studies of histological type of lung cancer have been reported for nonsmokers. For both males and females, adenocarcinoma appears to be the most common type, although the number of cases is too small to draw a definite conclusion (Tables VIII-18 and VIII-19). In studies in which smoking status is not specified, squamous cell carcinoma is the most frequent tumor type for males whereas in females, adenocarcinoma predominates (Tables VIII-20 and VIII-21). This distribution of types is similar to that seen in smoking populations—suggesting that the majority of these cases are in fact smokers. Table VIII-22 shows the data from studies in which both sex and smoking status were unspecified. These show an excess of squamous cell carcinomas, which probably reflects the proportion of male smokers in these groups.

It is clear from the foregoing that interpretation of studies relating histological type to occupation is difficult without information on sex and smoking status. However, despite these limitations certain occupational exposures do appear to exert an influence on the histogenesis of lung cancer.

Data relating cell type of lung cancer to occupation is shown in Table VIII-23. The pathology of lung cancer in cases with asbestos exposure and/or asbestosis has been studied (22) (52). These investigations indicate a relative increase in the number of adenocarcinomas. Asbestos associated tumors also tend to arise in areas of the lung most affected by asbestosis, i.e., peripherally in the lower zones (22) (39). Although a peripheral, lower lobe adenocarcinoma arising in an area of fibrosis may be considered to be a typical asbestos-associated lung cancer, the majority do not fall into this pattern. Thus in an individual case, knowledge of location or cell type has limited etiologic or medico-legal significance.

Several studies have shown a link between ionizing radiation, such as occurs in uranium miners and an increased frequency of small cell carcinomas (2)(33). Moreover, the relative frequency of this type of tumor increased with increased cumulative exposure to radiation (3)(33).

The lungs of uranium miners also showed a slight excess of severe atypia and early primary invasive carcinoma of the bronchial mucosa as compared to matched controls, although the prevalence of carcinoma *in situ* was approximately the same for the two groups (6).

An increase in small cell undifferentiated carcinomas in iron-ore miners (9)(15)(31) may also be due to moderate, but raised levels of radon within the mines, rather than the promoter effect of iron oxides on polycyclic aromatic hydrocarbons (34). A similar pronounced excess of small cell carcinomas has been observed in workers exposed to chloromethyl ether (50). There is also a dose-response effect. The authors concluded that small cell carcinoma was a specific response to chloromethyl ether exposure.

Significant but less impressive relationships have been observed in other occupations. Copper smelter workers exposed to arsenic appear to have a relative increase in adenocarcinomas as compared to the general population (51). In another group of copper smelter workers, an excess of poorly differentiated squamous cell carcinomas was observed (29).

Data for coal miners is conflicting: one study indicates almost equal proportions of the three major types of tumor (44) and another indicates an excess of squamous cell tumors (36). The populations were drawn from different geographic regions with either predominantly hard coal (anthracite) exposure (36) or predominantly soft coal (bituminous) exposure (44), and this may account for the differences observed.

There is no evidence to date to suggest that exposure to silica (32) or beryllium (40) exerts an influence on the histogenesis of lung cancer.

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Table VIII-16
HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
830	53	10			37	1956-65	U.S.A.	Autopsy	Weiss et al., 1977 (Cancer)
662	35	25	25	14	1	1955-72	U.S.A.	Autopsy	Auerbach et al., 1975 (Chest)
138	60	12	15		13	1955-70	U.S.A.	Autopsy	Sacomanno et al., 1971 (Cancer)
121	59	13	14	13	1	1955-70	U.S.A.	Autopsy	Archer et al., 1974 (Cancer)
1237	65	10			25	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-17
HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
46	54	26			20	1953-55	U.S.A.	Autopsy	Wynder et al., 1956
163	12	50	10		28	1947-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
72	31	21			48	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-18
HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
6		100				1955-72	U.S.A.	Autopsy	Auerbach et al., 1975
13	0	85			15	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-19
HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
50	32	58			10	1957-63	U.S.A.	Autopsy	Cooper et al., 1968
59	27	49			24	1953-55	U.S.A.	Autopsy	Wynder et al., 1956

Table VIII-20
HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
1228	52	11			37	1956-65	U.S.A.	Autopsy	Weiss et al., 1977
94	52	22	16	5	5	1956-65	U.S.A.	Autopsy	Weiss and Boucot, 1977
1186	37	25	21	16	1	1955-75	U.S.A.	Autopsy	Auerbach et al., 1979
152	75	9	9	7	0	1963-77	Irish Republic	Surgical	Healey, 1980
50	24	18	28	16	14	1954-71	U.S.A.	Autopsy & Surgical	Kannerstein and Churg, 1972
45	60	7	24	7	2	1954-72	U.S.A.	Autopsy & Surgical	Newman et al, 1976
42	47	12	14	19	7	1950-74	U.S.A.	Autopsy & Surgical	Wicks et al, 1981
1140	60	19			21	1941-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
1017	33	28	22		17	1958-77	U.S.A.	Autopsy & Surgical	Cox and Yesner, 1979
902	38	7			55	1933-48	England	Autopsy & Surgical	Mason, 1949
916	52	4	33		11	1948-52	England	Autopsy	Doll and Bradford, 1952
1404	42	24	18	9	8	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-21

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
98	11	13			76	193 -48	England	Autopsy & Surgical	Mason et al., 1949
79	23	13	48		16	1948-52	England	Autopsy	Doll and Bradford, 1952
164	26	38			36	1955-57	U.S.A.	Autopsy & Surgical	Haenszel et al., 1958
163	22	50			28	1947-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
201	16	31	12	22	19	1957-72	U.S.A.	Autopsy & Surgical	Beamis et al., 1975
278	20	38	24	12	6	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-22

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
231	42	20			38	1938-44	U.S.A.		Hollingsworth, 1947
1000	35	7			58	1933-48	England	Autopsy & Surgical	Mason, 1949
351	43	11	14		27	1942-51	U.S.A.		Collins, 1958
849	38	13	9		40	-48	U.S.A.	Autopsy & Surgical	McDonald et al., 1951
199	62	12	8		15	1933-58	U.S.A.	Biopsy & Surgical	Reinhoff et al., 1965
1309	63	11			27	1957-63	U.S.A.	Autopsy	Cooper et al., 1968
81	32	27	27	14	0	1963-77	Irish Republic	Autopsy	Healey, 1980
219	26	39	16		11	1963-76	U.S.A.	Autopsy & Surgical	Valaitis et al., 1981
1682	38	27	19	9	7	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-23
HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION SPECIFIED

Occupation/ Exposure	#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Smoking Status	Method of Diagnosis	Reference
Iron Ore Miners/Radon	69			37			1948-67	U.K.	NK	Autopsy	Boyd et al., 1970
Iron Ore Miners/Radon				44				France	NK	Autopsy	Roussel et al., 1964
Coal Miners (Anthracite)	165	79	10				1957-68	U.S.A.	I	Autopsy & Surgical	Scarano et al., 1972
Coal Miners (Bituminous)	202	24	31	28	9	8	1972-77	U.S.A.	S	Autopsy	Vallyathan et al., 1980
Free Silica	16	63	1	18			1960-67	Switzer- land	NS	Autopsy	Ruttner and Heer, 1969
Beryllium Workers	25	20	32	36	12	0	NK	U.S.A.	I	Autopsy & Surgical	Smith and Suzuki, 1980
Copper Smelter Workers/Arsenic	42	31	38	24	7	0	1950-74	U.S.A.	I	Autopsy & Surgical	Wicks et al., 1981
Copper Smelter Workers/Arsenic	25	56	12	28	4		1954-72	U.S.A.	I	Autopsy & Surgical	Newman et al., 1976
Copper Mine Workers	54	61	9	20	9	0	1954-72	U.S.A.	I	Autopsy & Surgical	Newman et al., 1976
Chloromethyl Ether Workers	28	3	18	68	7	3	1960-75	U.S.A.	S	Autopsy & Surgical	Weiss et al., 1979
Asbestos Workers	88	22	34	26	14	5	1962-72	U.K.	S	Autopsy & Surgical	Whitwell et al., 1974
Asbestos Workers	50	22	22	22	12	22	NK	U.S.A.	I	Autopsy & Surgical	Kannerstein and Churg, 1972
Uranium Workers	107	23	7	69		1	1950-70	U.S.A.	S	Autopsy	Archer et al., 1974
Uranium Workers	121	26		61		13	1950-	U.S.A.	S	Autopsy	Sacomanno et al., 1971

BA Bronchioloalveolar
 NK Not Known
 I Incomplete
 NS Nonsmokers
 S Smokers

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CLINICAL PRESENTATION

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James M. Melius

The clinical presentation of primary lung cancer due to either occupational or non-occupational causes is varied and depends on numerous factors including cell type, location and extent of tumor, and poorly defined host-tumor interactions. Some patients with lung cancer detected by routine chest radiographs will have no signs or symptoms. In other cases, particularly those with more central lesions, cough, hemoptysis, bronchial obstruction with secondary pneumonia, or other localized findings will be apparent. Intrathoracic spread may involve any structure, causing such symptoms as dyspnea due to pericardial or large pleural effusions, dysphagia due to esophageal compression or invasion, or hoarseness due to invasion of the recurrent laryngeal nerve. Metastasis outside the chest may involve any organ or structure with the most common sites being brain, liver, and bone. Alternatively, patients may present with nonspecific constitutional complaints as anorexia, weight loss, fatigue or weakness. Finally, primary lung cancers (particularly small cell carcinoma) may produce a number of paraneoplastic syndromes such as Cushing's syndrome, cerebellar degeneration, migratory thrombophlebitis, and nonbacterial thrombotic endocarditis.

DIAGNOSIS

The diagnosis of bronchogenic carcinoma usually centers around abnormalities seen on the chest radiograph. Special radiographic exams such as tomograms as well as old x-rays are often helpful in this clinical assessment. In general, cytologic or tissue diagnosis is obtained to confirm the clinical impression. Staging of the tumor is then necessary to determine the appropriate therapy. Interested readers are referred to the following excellent sources of comprehensive discussions of cancer staging:

American Joint Committee for Cancer Stag-

ing and End Results Reporting. "Staging of Lung Cancer, 1979." Chicago, Illinois.

D. T. Carr: Diagnosis and Staging. In: Lung Cancer, 1980. II World Conference, Copenhagen, Editors H. H. Hansen and M. Rorth. Excerpta Medica, Amsterdam, pp. 49-70.

Mountain, C. F., Carr, D. T., and Anderson, W. A. D. A System for the clinical staging of lung cancer. *Am J. Roent.* 120:130-38, 1974.

Numerous approaches and procedures have been used in the diagnostic evaluation of bronchogenic carcinoma, and each patient must be individualized. The underlying plan in all cases, however, is first to establish the diagnosis, then to determine the tumor's resectability (the chance that it can be totally removed surgically), and if resectible, to determine the patient's operability (the chance that he could survive post-resection cardiopulmonary function). Although the finding of small cell carcinoma is generally considered a contraindication to surgery, staging of this tumor can be useful in determining therapy and prognosis.

THERAPY

The primary mode of treatment of non-small cell bronchogenic carcinoma is surgical resection. Unfortunately, most patients are either unresectable or inoperable at the time of presentation. "Curative" radiotherapy has had some success in limited studies, but for the most part radiotherapy is used for palliation. It may relieve hemoptysis, superior vena cava obstruction, or brain or bone metastases. To date chemotherapy has had little permanent benefit. Combination therapy approaches have been and continue to be tried, including those using immunotherapy, but most well controlled studies again show little benefit.

Although the most lethal, small cell carcinoma is also the bronchogenic cancer most sensi-

tive to both chemotherapy and radiotherapy. Dramatic resolution of tumor masses can be obtained with either mode or with combination therapy. Except in rare cases, however, this remission is short-lived and cannot be maintained.

PROGNOSIS

The prognosis for bronchogenic carcinoma is poor, and unlike many other cancers, has changed little over the past 30 years. Overall five-year survival rates are less than 10%. Survival

is generally better with squamous cell carcinoma; it is much worse with small cell tumors.

Those asymptomatic patients who undergo surgical resection of small peripheral "coin" carcinoma can expect a five year survival rate of approximately 50%. On the other hand, those presenting with advanced disease may survive only a few weeks. While definite advances have been made in the treatment of patients with localized small cell cancer, the five year survival rate for this disease remains near zero.

MESOTHELIOMA

Ruth Lillis

DEFINITION

The primary malignant neoplasm of the pleura—diffuse pleural mesothelioma—has been recognized and accepted as a nosologic entity only during the last 20 years (77), although as early as 1767 Joseph Lieutand (cited by Robertson) reported two cases of probable mesothelioma among 3,000 autopsies, and E. Wagner described the pathology in 1870 (53)(72).

It is not known with certainty when the term “mesothelioma” was first used; one of the early reports indicating a primary and malignant tumor of the pleura and using the term mesothelioma was that by DuBray and Rosson (14).

In 1931, Klemperer and Rabin published a comprehensive description of the distinctive features of diffuse pleural neoplasms and recommended these tumors “should be designated mesothelioma,” since they arise from the surface lining cells of the pleura, the mesothelium (27). The malignant, diffuse pleural mesothelioma arises from the multipotential coelomic mesothelial cell of the pleura. Similarly, malignant tumors originating in the mesothelial cells of the peritoneum are peritoneal mesothelioma.

The definition of pleural mesothelioma thus includes:

- the origin of the tumor in the mesothelial cells of pleura
- the diffuse character of the tumoral growth, often involving a large surface or even the entire pleura of one lung, at the time of diagnosis
- the characteristic rapid growth and extension over the surface of the pleural serosa (closely related to the diffuse character)
- the high degree of malignancy, expressed in rapid growth, local invasiveness (soft tissue and bone structures of chest wall,

underlying lung, adjacent pericardium, regional lymph nodes), and frequent metastases to a variety of organs, including brain, liver, kidney, adrenals, etc. These characteristics of pleural mesothelioma have an integrative expression in the mean survival time after diagnosis, which does not exceed 12 months in most reported series, with or without therapeutic attempts.

The association between malignant “endothelioma of the pleura” (mesothelioma) and asbestos exposure was first reported by Wyers (80). Wagner et al., published a report on 33 cases of diffuse pleural mesothelioma from the North West Cape Province of South Africa; most of these cases had occurred over a four year period, and in all but one, exposure to asbestos (crocidolite) could be established (77). Mesothelioma was not necessarily preceded by asbestosis (interstitial pulmonary fibrosis); the exposure was occupational in some cases, but in others, only environmental (residential) exposure had occurred. The long latency period—a mean of 40 years—between initial asbestos exposure and the development of malignant pleural mesothelioma was another striking characteristic of these cases. The carcinogenic hazard of relatively low levels of asbestos exposure; the possibility that pleural mesothelioma associated with asbestos exposure may develop in the absence of preceding pulmonary interstitial fibrosis; and the long latency period between onset of exposure and development of the malignant mesothelioma, were thus outlined.

LIST OF CAUSATIVE AGENTS

Asbestos fiber is widely accepted as the causative agent in the vast majority of mesothelioma cases. So far, asbestos is the only fibrous mineral

where epidemiologic data have shown an association between exposure and pleural and peritoneal mesothelioma in man.

Asbestiform minerals are grouped in two major categories: chrysotile, which is a serpentine, and the amphiboles, which include crocidolite, amosite, anthophyllite, and tremolite.

The first large group of malignant pleural mesothelioma cases due to asbestos exposure was related to crocidolite in South Africa (77). This fact, and subsequent reports on mesothelioma cases from Great Britain where crocidolite had been extensively used, contributed to the empirical and one-sided view that crocidolite was the main or even the only type of asbestos with a specific carcinogenic potential resulting in the eventual development of mesothelioma.

The major increase in mesothelioma incidence in the United States—where chrysotile has been and still is the main type of asbestos used—supports a causal association between chrysotile exposure and development of mesothelioma (4)(31)(59)(63)(64). Epidemiologic evidence for worker cohorts has shown chrysotile to be equally as potent as other fiber types insofar as lung cancer is concerned (13)(49)(80). While the number of mesothelioma cases from populations exposed only to chrysotile has been small, an association with chrysotile exposure has been definitively established. Amosite has also been shown to have a similar carcinogenic effect; a significant number of mesothelioma cases have occurred in a cohort of 933 amosite factory workers(62). Experimental studies on rats using inhalation of five types of asbestos fiber resulted in the development of mesothelioma with chrysotile (Canadian), crocidolite, amosite, and anthophyllite (74). Previous experiments using intrapleural administration of amosite, chrysotile, and crocidolite had given similar results, with chrysotile giving the largest number of mesotheliomas, followed by crocidolite and amosite (73). Shabad et al. also reported on the experimental production of pleural mesothelioma in rats, with intrapleural administration of chrysotile (65). Thus, both epidemiologic evidence and experimental confirmation indicate that chrysotile, amosite, and crocidolite asbestos are causative agents for mesothelioma.

Recently another type of fibrous mineral—naturally occurring zeolites (aluminum silicates) of the fibrous variety (erionite, mordenite)—has come under close scrutiny as a potential causative agent

for malignant mesothelioma. The evidence for this association is based on the findings in a rural area of endemic mesothelioma in Turkey, where mineralogic investigations have not found any asbestos minerals, but have identified fibrous zeolites. Although this is still being actively researched and conclusive evidence is not yet resolved, fibrous zeolites are considered highly suspicious at the present time.

Reports on endemic mesothelioma in other parts of the world—such as in a rural area in India—have not yet identified the etiologic agent; the possibility that zeolites may be the causative agent cannot be excluded, since zeolites are known to be present in that area.

Experimental studies using intrapleural application suggest that other fibrous materials, such as fibrous glass, may also induce malignant mesothelioma (68). Epidemiologic evidence for fibrous glass as a causative agent for mesothelioma has not been reported, but fibrous glass has to be included as a suspected causative agent.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

Occupations and industries at risk to mesothelioma include all of those listed for asbestosis.

All available information indicates that mesothelioma may be the result of low levels and/or relatively short (of the order of several weeks to several months) asbestos exposure. The dose-response relationship for mesothelioma is therefore different than that for asbestosis (which develops with higher exposure levels over longer time periods) or bronchial carcinoma associated with asbestos exposure (which increases in incidence even after short periods of high asbestos exposure levels, but shows a marked increase in incidence with duration of exposure)(58). Since low asbestos exposure levels carry a significant risk of mesothelioma, occupations and industries characterized by relatively low asbestos levels (auto mechanics and brake repair, tapers in dry wall construction, handling of finished asbestos products including asbestos cement), while at relatively low risk for the development of parenchymal interstitial fibrosis (asbestosis), are nevertheless at high risk for mesothelioma.

Equally important is the fact that numerous workers in the various trades which do not simply direct asbestos exposure, such as electricians, painters, welders, carpenters, etc., in shipbuilding or ship repair, in construction, in maintenance

work at chemical plants, and even automobile salesmen supervising repair work, are frequently exposed to asbestos due to their mere presence in work areas where asbestos is being handled. This "bystander" exposure has been repeatedly documented to be responsible for numerous cases of mesothelioma (20)(51). It is therefore important to establish the principle that such indirect exposure carries a significant risk of mesothelioma.

Whitwell et al. found that 83% of mesothelioma cases reviewed contained over 100,000 asbestos fibers per gram of dried lung tissue; in cases of asbestosis the number of asbestos fibers was much higher, exceeding 3,000,000 per gram of dried lung tissue (79).

In shipyard workers, more and more mesothelioma cases have been reported; most of these have occurred in trades other than insulation workers, indicating that the risk is widespread (20)(61). The distribution of trades in private shipyards in the United States in 1943 is presented in Table VIII-24. A list of occupational titles in an Eastern U.S. shipyard in 1975 is given in Table VIII-25.

It is difficult to construct a complete list of all occupations in which asbestos exposure may occur at one time or another. Since short-term asbestos exposure (several weeks to several months) is often responsible for mesothelioma occurring 25, 30, 40, or 50 years later, the occupation/industry involved at the time of the diagnosis of a malignant tumor may differ from the occupation/industry where the exposure actually occurred. Therefore, at any point in time, much higher numbers of individuals are at risk for the development of mesothelioma than those working in industries and occupations known to be associated with asbestos exposure. Recollection of remote past exposures and of specific jobs in which they occurred is a formidable task, but crucial when assessing whether one particular case of mesothelioma is related to past asbestos exposure.

EPIDEMIOLOGY

The relationships between asbestos exposure and pleural mesothelioma regarding latency period, dose-response characteristics, populations at risk, and incidence of disease have been presented in the section—List of Occupations and Industries Involved, page 672.

Pleural mesothelioma is a rapidly progressing malignant tumor, the resulting disability is

Table VIII-24
PERCENTAGE DISTRIBUTION
OF TRADES IN PRIVATE SHIPYARDS
IN THE UNITED STATES, JUNE 1943

<i>Trade</i>	<i>Percentage</i>
Welders	15.3
Shipfitters	11.0
Machinists	8.1
Pipefitters	7.2
Electricians	6.6
Carpenters	6.1
Laborers	5.5
Burners	3.8
Painters	3.1
Sheetmetal workers	3.0
Riggers	2.8
Chippers and caulkers	2.8
Boilermakers	2.3
Crane operators	1.3
Pipe coverers	0.2
All other	21.1

Source: Bureau of Labor Statistics, Bulletin 824, "War-time Employment, Production, and Conditions of Work in Shipyards," 1945.

total, and the condition is usually fatal in one to two years. There are no confounding conditions or risk factors which limit the ability to establish cause-effect relationships.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk for developing mesothelioma includes:

- all occupations with direct contact and handling of asbestos.
- employees with other occupations (electricians, welders, painters, carpenters, etc.) who work or have worked—even for short periods—in areas where asbestos has been handled by others.
- family members (household contacts) of asbestos workers who have been exposed to asbestos fibers brought into the household by the worker. Household contamination has been found to result in asbestos exposure of family members of asbestos workers, sufficient in magnitude to induce mesothelioma (1)(2)(5)(32)(41)(46)(55)(56).
- individuals who have resided in the vi-

Table VIII-25
OCCUPATIONAL TITLES IN AN EASTERN U.S. SHIPYARD, 1975

Guard & Watchman	Heat Treater	Power House	Shipfitter
Construction	Tool Grinder	Engineer	Lead Bonder
Mechanic	Tool Room	Molder	Welder
Laborer	Attendant	Foundryman	Burner
Firefighter	Lathe Operator	Foundry Chipper	Rigger
Scrap Material	Miller	Melter	Sheetmetal Mechanic
Sorter	Drill Operator	Coremaker	Joiner
Painter	Grinder	Pipefitter	Carpenter
Painter Cleaner	Machinist	Silver Brazier	Industrial Radiography
Maintenance	Engraver	Pipcoverer	Technician
Painter	Layout	Electrician	Radiological Control
Truck Driver	Machine Rigger	Electronics	Monitor
Fork Lift Operator	Make Ready Man	Technician	Clerk
Warehouseman	Crane Operator	Maintenance	Data Processor
Transportation	Maintenance	Electrician	Secretary
Locomotive	Machinist	Loftsmen	Timekeeper
Operator	Dock Crew	Blacksmith	
Toolmaker	Inspector	Furnaceman	

cinity (one mile) of an asbestos plant, shipyard, or other source of asbestos contamination.

The population at risk at any point in time has to include all persons who have been exposed *in the past*. Given the long latency period between asbestos exposure and development of mesothelioma (on the average 35-40 years), individuals who have been exposed (even for short periods of time) during the last 50 years have to be considered potentially at risk.

Contributing to the population size at risk is (1) the fact that short duration of asbestos exposure (several weeks to several months) is sufficient to induce mesothelioma; (2) the high job mobility, especially during World War II; (3) the marked increase in the total amount of asbestos used per year; and (4) the diversification of its uses. The estimate of the population at risk is, for the same reasons, a complex and difficult task.

Attempts to assess the incidence of mesothelioma in populations at risk are also fraught with difficulties; these have multiple sources.

1. The complexity of the diagnostic criteria, which require pathologic confirmation; the most rigorous criteria make the diagnosis dependent on a complete autopsy (for the exclusion of another primary site of the tumor, which might have metastasized to the pleural cavity).

Only a proportion of all deaths are followed by a postmortem examination. This proportion varies with geographic area, with the time period considered, and with other factors.

2. Even when tissue specimens are examined by experienced pathologists, the diagnosis is not always simple; differences of opinion may persist and result in conclusions on the pathologic characteristics such as "possible mesothelioma" or probable mesothelioma."
3. Evaluation of the incidence of mesothelioma from death certificates has been reported, by all those who have investigated this problem, as incomplete, leading to a marked but quantitatively variable underestimate of the number of cases. This problem is compounded by the fact that the coding of causes of death does not provide a separate code for mesothelioma, but includes it with cancer of the lung or pleura.
4. The most reliable data are those based on the cohort approach: asbestos-exposed employees followed for many years, with a comprehensive assessment of causes of death. The long latency period between

onset of asbestos exposure and mesothelioma has resulted in a limited number of studies with a long enough follow-up period to realistically reflect its incidence. In all these cohort studies, most with several reports published over time, it is a rule without exception that the longer the observation period, the higher the incidence of mesothelioma.

Although the most relevant data on mesothelioma risk in asbestos-exposed populations are derived from long-term cohort studies, other studies following different approaches have also revealed the paramount importance of long-term follow-up and completeness of diagnostic means. The most significant information follows.

By 1965, 160 cases of mesothelioma had been recorded in the United Kingdom, 123 from England and Wales, 36 from Northern Ireland, and only one from Scotland (39). When a systematic review of all necropsy and surgical biopsy reports in all hospitals was undertaken, 80 cases of mesothelioma were found to have occurred in Scotland for the years 1950-1967. Many cases were in employees who had had no direct exposure to asbestos but had been employed in the shipbuilding industry, in a wide variety of trades.

The Mesothelioma Register in Great Britain (Employment Medical Inspector's Advisory Service)—with data sources in death certificates, Cancer Bureau registrations, Pneumoconiosis Medical Panels (claims for benefits under the National Insurance Acts), chest physicians, surgeons, pathologists and coroners—had 413 cases reported for 1967-1968; 75% of the confirmed cases with definite asbestos exposure came from shipbuilding, asbestos factories, and insulation work; the other 25% from a variety of occupations (welders, electricians, gas workers, mechanics, chemical workers, etc.). The highest rate/million per year of mesothelioma (confirmed cases) figures were 8.93 and 8.24, both in shipbuilding areas. The incidence of definite mesothelioma in the United Kingdom for the period 1967-1968 was 120 per year. It was concluded that this figure may considerably understate the true incidence.

McDonald and McDonald reviewed evidence published between 1959 and 1976, including cohort studies of asbestos workers; "population studies" (mesothelioma surveys in Canada and the United States describing "case-series

referable to some kind of denominator"); case reports unrelated to any denominator; and mortality statistics, mainly in Canada, the United States, and the United Kingdom (37). Data from the Third U.S. National Cancer Survey (42) was also reviewed. A total of 4,539 cases had been published after 1958. (This figure did not include cases from official mortality statistics and Third U.S. National Cancer Survey.) The incidence of mesothelioma for the period preceding 1958 had been very low: in 1957 Hachberg mentioned 43 cases in 60,042 autopsies over the 40-year period, 1910-1949, i.e., less than 1 case per year and only 0.07% of the autopsies performed (Philadelphia, Baltimore, Minneapolis, New York, and Toronto in North America and Munich, Prague, and Copenhagen in Europe).

The marked increase in the incidence of mesothelioma over the last 20 years is evident when comparing the total number of reported cases (436) for the period 1955-1959, with that of 1,697 cases of mesothelioma for the period 1965-1969 (an almost fourfold increase). Interestingly, 9% of cases were due to neighborhood or household-family exposure.

In the Third National Cancer Survey (1975), a thorough ascertainment was done using hospital records and pathology material, besides death certificates, in selected areas comprising approximately 10% of the population of the United States (deaths in 1971). The annual rate per million for males 45 and over was 11.20 and for females in the same age range, 3.53.

Reports from other countries, such as Germany, Sweden, the Netherlands and Great Britain, indicate much higher rates than those published for Canada by McDonald (10 per million for males and 4 per million for females, over 45-years-old) for some cities and regions, most with large shipyards: Walcheren had a death rate 23.3 times higher than that expected according to the Canadian rates; Wilhelmshaven (21.5 times higher); Plymouth (14.3 times higher); and Rotterdam, Harlem, Hamburg, Malmo, Nantes, and Trieste (with rates 7-8 times higher) (38)(51)(69). These data indicate that annual incidence rates for mesothelioma in geographical areas with shipyards and/or other important asbestos industries or uses are of the order of 200/1 million or higher, for men aged 45 or over.

The most relevant data on the incidence of mesothelioma in exposed populations are derived from cohort studies of occupational groups. But

only studies with long follow-up (30-40 years) can provide comprehensive information, although even these might not include all the cases. It has been estimated, from the relatively limited number of such studies, that between 5% and 11% of all deaths in asbestos-exposed workers are due to mesothelioma (16)(26)(43)(45)(61)(62)(63). In a cohort of 632 asbestos insulation workers observed prospectively from January 1, 1943 to December 31, 1976, 38 out of a total of 478 deaths were due to mesothelioma (see Table VIII-26) (60). The mortality experience of a large cohort of 17,800 asbestos workers in the United States and Canada (Table VIII-27) observed from 1967 to 1977 indicates that 175 out of 2,270 deaths were due to mesothelioma. In a cohort of amosite asbestos factory workers employed from 1941-1945, and observed until 1977, 16 out of 594 deaths were due to mesothelioma (Table VIII-28) (62). In another cohort of 689 asbestos factory workers employed before January 1939, and observed from 1959 through 1975, 26 out of 274 deaths were due to mesothelioma (48)(60). Newhouse reported the mortality experience of workers in an East London asbestos factory, 1931-1970; out of a total of 461 deaths, 35 were due to mesothelioma (43).

The importance of long-term observation is shown in Tables VIII-29, VIII-30, and VIII-31.

Two further problems are: 1) the correct assessment of all those at risk for developing mesothelioma in various occupations, or who have had such exposure even for short periods of time sometime during the last 40-50 years; and 2) quantification of the risk for "bystander" exposure, neighborhood or other types of environmental exposure (buildings, schools, etc.), and household-family exposure.

Although no firm data are as yet available for these types of asbestos exposure, according to the information available on cases occurring after short (several weeks) and relatively low levels of exposure, it has to be assumed that the risk is of the same order of magnitude as that for occupationally-exposed groups.

PATHOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

The pathology of mesothelioma is largely determined by the potential of the mesothelial cells to produce tumors of epithelial, mesenchymal, or most commonly a mixed type. This potential is related to the embryologic origin of the mesothelium, which is derived from coelomic epithelium developed from the mesoderm and

underlined by mesenchymal tissue (27).

The macroscopic features of pleural mesothelioma are those of a gray-white or yellow-gray mass, varying in extent from a part of the lung's surface to a complete, or almost complete, encasement of the lung. The tumor has a rapid growth rate, extending along the serosa, with a tendency to grow along the interlobar fissures. Both the parietal and visceral pleura are involved; often the tumor seems to have originated in the visceral pleura (for example, in the minor fissure).

Two types of mesothelioma can be observed: 1) the scirrhous type, presenting as a hard sheet, with variable thickness often exceeding one inch, rapid encasement and compression of the lung, partial or total obliteration of the pleural cavity, and contraction of the hemithorax; and 2) the encephaloid type, presenting as large tumor masses, often multiple, sometimes with extremely rapid growth (seen on chest x-rays as "scalloping").

Continuous spread—with local invasion of the pericardium, mediastinum, chest wall, diaphragm, and, through it, the liver and peritoneum, or into the contralateral pleura—is frequent. The underlying lung can be invaded directly, into the pulmonary parenchyma immediately underlying the pleura, or by spread into septal and perivascular lymphatics, with lymph node involvement in about 50% of cases. Distant metastases, thought in the past to be rare, are, on the contrary, quite frequent, affecting the brain, liver, kidney, adrenals, thyroid, lung, or other organs in more than 50% of cases. Tumor growth along the needle biopsy track or surgical scar after thoracotomy is common.

Microscopic features are characterized by diversity of appearance, not only from case to case, but also in the same tumor, where both epithelial (or tubulo-papillary) and mesenchymal (or fibrosarcomatous) areas can be observed. According to the microscopic pattern, mesothelioma can be classified into four types: 1) epithelial or tubulo-papillary, with the epithelial cells usually cuboidal or flattened, tending to form tubular and papillary structures, separated by a more or less abundant matrix; 2) mesenchymal or fibrosarcomatous, appearing as a spindle cell sarcoma, but sometimes with extensive areas of acellular collagen; 3) mixed, the most frequent form, containing both epithelial and fibrosarcomatous areas; 4) the undifferentiated type, with polygonal, less often spheroidal cells, with large nuclei and scanty mitotic figures. These cells resemble those of the tubulo-papillary

Table VIII-26

EXPECTED AND OBSERVED DEATHS AMONG 632 NY-NJ ASBESTOS INSULATION WORKERS OBSERVED PROSPECTIVELY JANUARY 1, 1943 - DECEMBER 31, 1976

	Number of Men	632
	Man-years of observation	13,925
	<i>Deaths 1.1.43-12.31.76</i>	
<i>Cause of death</i>	<i>Expected*</i>	<i>Observed</i>
<i>Total deaths, all causes</i>	328.9	478
<i>Total cancer, all sites</i>	51.0	210
Lung cancer	13.3	93
Pleural mesothelioma	**	11
Peritoneal mesothelioma	**	27
Cancer of esophagus	1.4	1
Cancer of stomach	5.4	19
Cancer of colon - rectum	8.3	23
All other cancer	28.06	36
<i>Asbestosis</i>	**	41
<i>All other causes</i>	262.6	227

*Expected deaths are based upon age and sex-specific U.S. death rates of the National Center for Health Statistics, 1949-1975 actual rates, 1943-1948 extrapolated from 1949-1955 rates, and 1976 extrapolated from 1967-1975 data.

**These are rare causes of death in the general population.

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Table VIII-27

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967 — JANUARY 1, 1977

	Number of Men	17,800	
	Man-years of observation	166,855	
	<i>Expected*</i>	<i>Observed</i>	<i>Ratio</i>
<i>Total deaths, all causes</i>	1,660.96	2,270	1.37
<i>Total cancer, all sites</i>	319.90	994	3.11
Lung cancer	105.97	485	4.58
Pleural mesothelioma	**	66	—
Peritoneal mesothelioma	**	109	—
Cancer of esophagus	7.01	18	2.57
Cancer of stomach	14.23	22	1.55
Cancer of colon - rectum	37.86	59	1.56
All other cancer	154.83	235	1.52
<i>Asbestosis</i>	**	162	—
<i>All other causes</i>	1,351.06	1,114	0.82

*Expected deaths are based upon white male age-specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.

**These are rare causes of death in the general population.

Table VIII-28
EXPECTED AND OBSERVED DEATHS
AMONG 933 AMOSITE FACTORY WORKERS EMPLOYED
1941-1945, OBSERVED TO DECEMBER 31, 1977

<i>Deaths 1941-1977</i>			
	<i>Expected^(a)</i>	<i>Observed</i>	<i>Ratio</i>
<i>Total deaths</i>	368.62	594	1.61
<i>Cancer, all sites</i>	73.35	195	2.66
Lung cancer	19.16	100	5.22
Pleural mesothelioma	^(b)	8	—
Peritoneal mesothelioma	^(b)	8	—
G.I. cancer	21.55	32	1.48
All other cancer	32.64	47	1.44
<i>Asbestosis</i>	^(b)	30	—
<i>Other noninfectious respiratory disease</i>	8.47	19	2.24
<i>All other causes</i>	286.80	350	1.22

^(a) Expected deaths based upon age-specific death rate data for New Jersey white males in corresponding years. In 4 cases, ages were not known; omitted from calculations. 39 men partially traced and 890 traced to death on December 31, 1977.

^(b) Death rates not available, but these have been rare causes of death in the general population.

type.

A property of mesothelial cells is the production of acid mucopolysaccharides, especially hyaluronic acid, which stains strongly with colloidal iron, but not with periodic acid Schiff (PAS). This last characteristic is useful in differentiating mesothelioma from adenocarcinoma; the latter usually gives a positive stain with PAS. The hyaluronidase test (digestion of hyaluronic acid by the enzyme) is useful in a limited number of cases, since the tubulopapillary type of the tumor is the only form which consistently produces hyaluronic acid. Therefore a negative hyaluronidase test does not exclude the diagnosis of mesothelioma.

The pathogenesis of mesothelioma is not yet completely understood. Nevertheless, the following facts of major theoretical and practical consequence have been established:

- mesothelioma may result from exposure to crocidolite, chrysotile and/or amosite; the evidence is derived from epidemiologic and experimental animal studies.
- relatively low levels and short duration of exposure can produce mesothelioma.

- while a dose-response relationship may exist, it has not been quantitatively clarified, and therefore available information can only be interpreted to indicate that any asbestos exposure, given a long enough period of follow-up, may induce mesothelioma.
- the hypothesis according to which polycyclic aromatic hydrocarbons adsorbed on asbestos fibers are important in the induction of mesothelioma has not been confirmed, nor has that attributing a similar effect to adsorbed trace metals (19).
- cigarette smoking has no etiologic relationship with mesothelioma.
- in experimental studies, intrapleural administration of asbestos, but also of similarly sized fibers of fibrous glass and fibrous aluminum oxide, resulted in pleural mesothelioma (66)(67)(68). This seems to indicate that fibrous characteristics, rather than the chemical composition, are crucial for this specific carcinogenic effect.
- a special selectivity in the distribution of asbestos fibers, relevant to the problem

Table VIII-29
EXPECTED AND OBSERVED DEATHS AMONG 689 ASBESTOS FACTORY WORKERS,
EMPLOYED BEFORE JANUARY 1, 1939 DURING THE SEVENTEEN YEARS
FROM JANUARY 1, 1959 THROUGH DECEMBER 31, 1975

	1959-1964		1965-1970		1971-1975		1959-1975		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs./Exp.
<i>All causes</i>	59	52.41	123	69.85	92	65.93	274	188.19	1.46
<i>Cancer, all sites</i>	21	10.47	45	14.70	33	14.73	99	39.92	2.47
Lung cancer	6	2.96	18	4.65	11	4.92	35	12.53	3.91 ^a
Pleural mesothelioma	1	n.a.	5	n.a.	7	n.a.	14	n.a.	—
Peritoneal mesothelioma	1	n.a.	6	n.a.	4	n.a.	12	n.a.	—
Cancer of esophagus, stomach, colon and rectum	4	2.23	5	2.92	3	2.83	15	7.99	1.88
Cancer, all other sites	9	5.28	11	7.13	8	6.98	23	19.40	1.19
<i>All respiratory disease</i>	14	3.01	10	4.56	18	4.60	42	12.16	3.45
Asbestosis	12	n.a.	8	n.a.	15	n.a.	35	n.a.	—
Other respiratory	2	(b)	2	(b)	3	(b)	7	(b)	—
<i>All other causes</i>	24	38.93	68	50.59	41	46.60	133	136.11	0.98
Person-years of observation	3,962		3,411		2,273		9,646		

(a) Pleural mesothelioma included with cancer of bronchus in calculating ratio since expected rates are based upon "cancer of lung, pleura, bronchus, trachea."

(b) This rate is virtually identical with that of "all respiratory disease."

n.a.—not available.

Table VIII-30
MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS
IN THE UNITED STATES AND CANADA 1967-1977:
OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

	Number of men		17,800							
	Man-years		166,855							
	<i>Duration from onset of work exposure (years)</i>									
<i>Cause of death</i>	<i>Total</i>	<i><10</i>	<i>10-14</i>	<i>15-19</i>	<i>20-24</i>	<i>25-29</i>	<i>30-34</i>	<i>35-39</i>	<i>40-44</i>	<i>45+</i>
<i>All causes</i>	2,270	51	85	188	320	388	340	253	203	442
<i>Cancer, all sites</i>	994	7	17	59	125	193	186	128	95	184
Lung	485	0	7	29	59	104	112	66	39	69
Pleural mesothelioma	66	0	0	2	6	15	10	16	4	3
Peritoneal mesothelioma	109	0	0	3	3	18	22	18	16	29

Table VIII-31
EXPECTED AND OBSERVED DEATHS
AMONG 933 AMOSITE ASBESTOS FACTORY WORKERS EMPLOYED 1941-45
OBSERVED TO DECEMBER 31, 1977

<i>Deaths of lung cancer and mesothelioma</i>						
<i>Time from onset (years)</i>	<i>Man-years</i>	<i>Lung cancer</i>			<i>Mesothelioma</i>	
		<i>Exp.</i>	<i>Obs.</i>	<i>Ratio</i>	<i>Pleural</i>	<i>Peritoneal</i>
<5	4,331	0.95	0	—	0	0
5-9	4,095	1.78	3	—	0	0
10-14	3,784	2.57	13	5.06	0	0
15-19	3,362	3.19	20	6.27	0	0
20-24	2,837	3.49	18	5.16	1	0
25-29	2,250	3.59	25	6.96	2	4
30-34	1,553	3.16	17	5.38	5	3
35+	192	0.41	4	—	0	1
	22,404	19.14	100	5.22	8	8

of mesothelioma induction, has been demonstrated by Roe et al. (54). After subcutaneous injection in mice (experiments with three types of asbestos), wide dissemination from the site of injection and a highly selective distribution were observed; the main sites of asbestos accumulation were the visceral and parietal pleura and the serosal surface in the abdominal cavity.

- the fiber size (cross-sectional diameter and length) seems to be important, since smaller fibers penetrate deeply into the periphery

of the lung and subpleural areas (21)(22)(67)(68)(70)(75).

The evidence for marked effects, including the carcinogenic mesothelioma inducing effect of small fibers (length less than 5 μ m) has emerged relatively recently (122)(24)(75). This is important in view of the fact that handling or treating asbestos as well as use of asbestos products generates fragmentation (both longitudinally and transversely) of fibers resulting in a larger number of shorter and thinner fibers or even fibrils. Chrysotile is especially prone to undergo such

fragmentation.

CLINICAL DESCRIPTION

Symptoms

Chest pain (unilateral) and shortness of breath are the most common presenting symptoms. The chest pain may be diffuse and dull or it may be of the pleuritic type; it often progresses to be severe. Shortness of breath may rapidly progress, especially with the development of a pleural effusion.

Other relatively frequent symptoms are loss of appetite, weight loss, fatigue, and in some cases fever; cough is infrequent.

Physical Signs

Pleural effusion occurs in the majority of cases, with dullness on percussion and decreased breath sounds. Rapid recurrence after aspiration of pleural fluid is the rule. The pleural fluid may be serous and clear but sometimes is hemorrhagic.

Retraction of the affected hemithorax, and shifting of the mediastinum to the side of the lesion may occur.

Natural History

Rapid tumor growth—often after pleural biopsy, i.e., needle biopsy or thoracotomy—with subcutaneous tumor nodules may involve the chest wall, the ribs and vertebrae, the mediastinum (sometimes with superior vena cava syndrome), and/or the pericardium with pericardial effusion. Distant metastases to the liver or other intra-abdominal organs, sometimes with ascites, can be clinically detected.

The metastatic spread of mesothelioma is much more frequent than previously thought and has been shown to occur in the majority of cases in which an autopsy was performed; both lymph node metastases and distant hematogenous metastases can be found. Spread of the mesothelioma to the opposite pleural cavity, and also to the peritoneum, is frequent; most often this is the result of a local invasive process, through the mediastinum or through the diaphragm.

The natural history of the disease is that of a rapid downhill course; death occurs in the majority of cases after an interval of months to one or two years. The mean survival from first diagnosis does not exceed 12 months. Although all therapeutic methods have been used, often in combination (surgery, radiotherapy, chemotherapy), no significant difference in survival of pa-

tients with pleural mesothelioma has been consistently achieved.

Laboratory Investigations

Radiographic changes are characteristically unilateral and progressive. The two main modalities of radiologic changes in pleural mesothelioma are: 1) unilateral pleural effusion; 2) large, nodular, protuberant opacities projecting from the pleura into the pulmonary parenchyma. Most often a combination of these changes is found.

Aspiration of the pleural fluid may be helpful in revealing underlying solid tumoral opacities. Extension of the tumoral growth over the apical pleura and into the mediastinal pleura is frequent. PA chest radiographs should be complemented by oblique views of the chest whenever a suspicion of pleural mesothelioma arises. Other radiographic evidence of asbestos-related parenchymal and/or pleural changes may or may not be present. Pleural plaques or calcifications are a useful marker of past asbestos exposure.

Pulmonary function studies are irrelevant for the diagnosis of mesothelioma.

Pleural fluid aspiration, while often necessary to alleviate respiratory distress, is of limited diagnostic use. Cytology of the pleural effusion is often fraught with the difficulty of distinguishing between mesothelial malignant cells and "atypical" mesothelial cells. The detection of hyaluronic acid in the pleural fluid is useful, although it can be found with other malignant tumors of the pleura; a negative result does not discard the diagnosis (6)(25)(76).

Needle biopsy specimens are insufficient for tissue diagnosis, since tissue specimens so obtained might not include malignant changes (although such changes may well be present in adjacent areas of the pleura) and since there is marked variability of pathologic changes.

Thoracotomy with surgical pleural biopsy, although providing adequate tissue specimens for diagnostic purposes, is often followed by local extension of tumor growth into the chest wall.

Treatment

There is no effective therapeutic approach, although surgery to reduce the tumor mass (9), radiotherapy (17)(57)(71), chemotherapy, single drugs (7)(18)(29)(30)(40), or combinations of two, three, or four drugs, and all possible combinations of these methods have been attempted (35).

Wanebo et al. reported on 66 cases with

malignant mesothelioma (78). For the epithelial type, pleurectomy combined with irradiation and chemotherapy seemed to be more effective; in the fibrosarcomatous type, surgery resulted in longer survival.

Prognosis

The disease is fatal, and progression is usually rapid, with marked deterioration over short periods of time. In exceptional cases, longer survival (several years) can occur even in the absence of any therapeutic procedure.

DIAGNOSTIC CRITERIA

The diagnostic criteria for pleural mesothelioma are:

- a history of asbestos exposure in the past. Occupational exposure (even for short periods) or household or neighborhood exposure has to be actively searched for and can be established in the vast majority of cases if histories are taken by a physician with experience in occupational medicine (11).
- long latency period, usually more than 20 years from onset of exposure, most often between 30 and 40 years.
- clinical symptoms: unilateral chest pain and/or significant increase in dyspnea over a short period of time (weeks or months).
- physical findings: consistent with pleural effusion.
- radiographic abnormalities presenting as pleural effusion or pleural thickening often with large nodular opacities projecting from the pleura. Rapid increase in pleural thickening or the appearance of irregularities of the pleura are highly suspicious. Rapid progression of radiologic changes.
- tissue diagnosis on an adequate specimen (thoracotomy with pleural biopsy). Microscopic findings consistent with the epithelial (tubulopapillary), mesenchymal (fibrosarcomatous), or mixed or undifferentiated type.

The complexities and difficulties of the pathologic diagnosis have been discussed. The finding of hyaluronic acid in the pleural fluid of tissue specimen is useful, but the diagnosis cannot be discarded when the test is negative.

In the differential diagnosis of pleural mesothelioma, the following problems are of practical importance: (a) Benign pleural effusions may occur in a patient with present or past asbestos exposure. The clinical course is usually indicative, since benign pleural effusions tend to resolve spontaneously over several weeks. Nevertheless, such a "benign pleural effusion" has been observed, in some cases, to be a precursor of pleural mesothelioma. (b) Pleural fibrosis is a common finding in persons with present or past asbestos exposure; the prevalence increases with time since onset of exposure. In cases with extensive pleural fibrosis, especially when the width on chest x-ray exceeds 10 mm, the differential diagnosis between pleural fibrosis and pleural mesothelioma may be difficult. The presence of similar pleural changes on previous x-ray films makes the diagnosis of mesothelioma less likely; repeat chest x-ray films after several weeks are necessary when no previous chest x-ray are available. (c) The differential diagnosis between pleural mesothelioma (*primary* malignant tumor originating in the pleura) and secondary involvement of the pleura by a malignant tumor, either lung cancer or another primary malignant tumor with metastatic spread to the pleura, has been given much attention. In the case of lung cancer, sputum cytology and fiber optic bronchoscopy with bronchial biopsy, in addition to the radiologic appearance, contribute to the differential diagnosis. The proportion of cases which remain undecided is small. The possibility of a malignant primary tumor originating in another site, with metastatic spread to the pleura is investigated by the routine clinical work-up. Patients with no other detectable primary tumor but with clinical and radiologic features of mesothelioma have, with a high degree of probability, pleural mesothelioma. The absolute certainty of this differential diagnosis is reached only after postmortem examination.

In reviewing the experience accumulated over the last 20 years, it becomes obvious that pleural mesothelioma has been largely undiagnosed in the past. This has been established in prospective cohort studies of asbestos-exposed workers (28)(33)(34)(38)(44)(47)(60); in many studies investigating diagnostic accuracy in series of reported mesothelioma cases (15); and in systematic reviews of all pathology material—as in Scotland where 80 undiagnosed cases were discovered (39).

In the 1967-1977 cohort study of 17,800 asbestos insulation workers in the United States and Canada, out of a total of 2,270 consecutive deaths, 60 were recorded on the death certificate as mesothelioma (31 pleural, 29 peritoneal). Review of medical records, including pathology reports, chest x-ray films, postmortem examinations (when available) and independent review of tissue specimens by experienced pathologists resulted in a diagnosis of mesothelioma in 175 cases (66 pleural, 109 peritoneal). The death certificate accuracy was 47% for pleural mesothelioma and 27% for peritoneal mesothelioma (Table VIII-32). In another cohort of 689 asbestos workers, 11 cases of mesothelioma (4 pleural, 7 peritoneal) were recorded on death certificates for the period 1959-1975. Review of medical records and pathology material resulted in a diagnosis of mesothelioma in 26 cases (14 pleural, 12 peritoneal), with the death certificate accuracy only 28% for pleural mesothelioma, and 58% for peritoneal mesothelioma (Table VIII-33).

In the majority of pleural mesothelioma cases it is possible to establish the diagnosis *intra vitam*. The greater awareness of population groups with present or past exposure, of the Department of Health, Education and Welfare, of other governmental agencies, and of the medical community are expected to result in earlier diagnosis. This is a prerequisite for future meaningful attempts of therapy.

The requirement of postmortem examination for the definitive diagnosis is necessary for the complete assessment of mesothelioma incidence from an epidemiologic point of view, although it is expected that a higher index of suspicion will substantially reduce the difference between the number of cases diagnosed while alive and those in which the diagnosis is reached only after postmortem examination.

METHODS OF PREVENTION

The prevention of pleural mesothelioma is dependent on the reduction of exposure to asbestos fiber to the minimum possible level, since this adverse health effect has been specifically associated with low level and short-term exposure. In December 1976, NIOSH, based on a "Reexamination and Update of Information on the Health Effects of Occupational Exposure to Asbestos," recommended to the DHEW and OSHA that the standard be reduced to 0.1 fibers/cm³. This was

based on the lowest concentration at which asbestos fibers can be reliably identified by phase contract microscopy.

RESEARCH NEEDS

Critical problems where research is needed:

1. Determine mechanisms of carcinogenicity (mineral fibers; potential effect of other mineral fibers, such as zeolites, titanite fibers, etc.).
2. Define, to the extent that it is at all possible, the lowest level of asbestos exposure which may result in mesothelioma. This is of paramount importance for the acceptable standard.
3. Establish the role(s) of immune mechanisms in individual susceptibility for mesothelioma.
4. Determine mechanisms of carcinogenicity in peritoneal mesothelioma, including the significance of ingestion of fibers. This is important since water may be polluted with mineral fibers from various sources, and the risk of mesothelioma from such a situation has not yet been assessed.
5. Establish mesothelioma therapy.

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Table VIII-32

**MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS
IN THE UNITED STATES AND CANADA 1967-1977:
OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS**

<i>Cause of death</i>	<i>Accuracy of death certificate categories</i>				
	<i>Expected</i>	<i>Death Certificate</i>		<i>Ascertained</i>	
		<i>Number</i>	<i>o/e</i>	<i>Number</i>	<i>o/e</i>
<i>Cancer, all sites</i>	319.90	888	2.77	994	3.10
Cancer, lung	105.97	403	3.80	485	4.57
Pleural mesothelioma	—	31	—	66	—
Peritoneal mesothelioma	—	29	—	109	—
Cancer, esophagus	7.01	16	2.28	18	2.56
Cancer, stomach	14.23	19	1.34	22	1.55
Cancer, colon	37.86	58	1.50	59	1.56
Cancer, pancreas	17.46	48	2.75	22	1.26
Cancer, liver	7.50	18	2.40	5	0.66
Cancer, brain	10.34	19	1.84	14	1.35
<i>Asbestosis</i>	—	108	—	162	—
<i>Chronic obstructive lung disease</i>	58.58	127	2.17	66	1.13

Death certificate accuracy: Cancer, 89%; lung cancer, 83%; G.I. cancer, 94%; pleural mesothelioma, 47%; peritoneal mesothelioma, 27%.

Table VIII-33

**RELATION BETWEEN DIAGNOSIS OF CAUSE OF DEATH AS RECORDED
ON THE DEATH CERTIFICATE AND AS ASCERTAINED BY REVIEW
OF ALL AVAILABLE INFORMATION, IN 274 DEATHS AMONG 689
ASBESTOS WORKERS OBSERVED JANUARY 1, 1959 - DECEMBER 31, 1975**

	<i>Death certificate</i>	<i>Ascertained</i>
<i>Cancer, all sites</i>	94	99
Cancer of lung	36	35
Pleural mesothelioma	4	14
Peritoneal mesothelioma	7	12
Mesothelioma — unspecified site	7	0
Cancer of esophagus, stomach, colon, and rectum	12	15
All other cancer	28	23
<i>All respiratory disease</i>	43	42
Asbestosis	26	35
Pneumoconiosis	8	0
All respiratory disease	9	7
<i>All other causes</i>	137	133

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SCREENING

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Desirable features of a detection program for early cancer include a high prevalence of detectable pre-clinical disease in the target population and a treatment regime for screen-detected cancer stage that is more effective than therapy at later stages. Moreover, screening procedures should exhibit high degrees of sensitivity and specificity. Screening must be considered a composite of the actual testing program as well as the consequences resulting from the outcome of each screening procedure. As such, early cancer detection programs are associated with many direct and indirect costs, such as screening, definitive diagnosis, treatment, follow-up and lost earnings, which ought to be reasonable in relation to total health expenditures and anticipated health benefits (3).

Changes in morbidity and mortality are potential indices for the assessment of benefit from screening. Of these, mortality is preferred owing to its objectivity and easy measurement. Case survival is frequently used to assess benefit from screening, but it is an unacceptable evaluation measure if uncorrected for the specific biases to which it is susceptible. Increased case survival may reflect advancement of diagnosis by screening (lead time bias) or bias toward slower-growing, less malignant tumors (length bias) rather than a true postponement of death (4)(2)(10). Selection and observation biases are additional non-random factors which may influence any index of benefit assessment.

Clinical trials in lung cancer screening have employed chest roentgenograms, alone or in combination with sputum cytology. These have shown the chest radiograph to be more sensitive than sputum cytologic examination. Its sensitivity, nonetheless, is low (24-82%) as it is only capable of detecting lesions at least one centimeter large (7)(11). In contrast, sputum cytology may be slightly more specific than the chest x-ray. There appears to be little overlap, however, between these tests in lung cancer screening. Chest

radiographs are of greater benefit in the detection of peripheral tumors and sputum cytology tends to identify radiographically occult central or hilar malignancies (7)(6)(5)(9).

Studies employing one or both of these tests at variable intervals have established that: first, more lung cancers are discovered in screened versus nonscreened groups; second, screen-detected neoplasms exhibit a greater shift toward early stage tumors; and third, case survival tends to be greater among those with screen-detected malignancies (7)(6)(12)(9). A screen-discovered, early lesion with increased case survival, however, does not necessarily equal a cancer cured or a death postponed. The desired outcome of lung cancer screening is usually the demonstration of a reduction in mortality. To date no clinical trial, including the ongoing National Cancer Institute randomized studies, has shown that screening for lung cancer accomplishes this goal. While detection programs have not been adequately examined in high risk occupational groups, one can expect that such a population will only exhibit an increased prevalence of detectable pre-clinical disease rather than provide a different outcome. Caution must be exercised, therefore, in the commitment of increasingly scarce resources to large scale routine screening for lung cancer—given present knowledge.

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SECTION IX
INFECTIOUS DISEASE



INHALATION ANTHRAX

Philip S. Brachman

DEFINITION

Anthrax is a zoonotic disease caused by *Bacillus anthracis*, which in humans has three primary forms: cutaneous, inhalation, and gastrointestinal. In the United States, over 95% of reported cases have been the cutaneous form and 5% the inhalation form; no adequately documented cases of the gastrointestinal form have been reported (2). Since 1955 approximately 80% of the cases have been industry related and 20% agriculture related.

Inhalation anthrax is an acute disease of humans resulting from the inhalation of *B. anthracis* spores with the subsequent development of hemorrhagic mediastinitis, toxemia, and septicemia; it is usually fatal. Cases are either directly or indirectly related to an industry which processes *B. anthracis* contaminated animal products (3). The disease has been called wool-sorters' disease because historically it was usually an occupational disease involving workers who sorted wool and less frequently goat hair (10). However, workers who became ill were, for the most part, sorting imported goat hair when they became infected. At times the disease is referred to as pulmonary anthrax. This implies that the disease is primarily a disease of the lungs and this is incorrect. There can be secondary involvement of the lungs, but the primary involvement is of the mediastinal lymphatic system.

CAUSATIVE AGENT

The disease is caused by *B. anthracis*, a gram-positive, spore-forming bacillus that grows well on ordinary laboratory media (i.e., 5% human blood agar), has distinctive growth characteristics, and can be further identified by susceptibility to *B. anthracis* bacteriophage and fluorescent-antibody staining. Characteristically, the organism forms spores which are moderately resistant to destruction; the ability of these spores to remain viable for many years in soil and the

industrial environment is an important factor in the epidemiology of anthrax.

OCCUPATIONS AT HIGH RISK

Inhalation anthrax has occurred among individuals employed in industries in which aerosols contaminated with *B. anthracis* are generated by the processing of imported goat hair, wool, and hair from various other animals (including horses and alpacas), as well as hides, skins, and dried bones. In the United States, goat hair imported from Asian countries has caused the most cases of inhalation anthrax. The most frequent use of goat hair is in preparation of thread which is woven into a hair cloth interlining used in clothing. Goat hair may also be processed into a felt material used as underpadding in the carpet industry, as insulation material in the plumbing industry, and as polishing wools, saddle pads, and washers. Jobs most frequently associated with inhalation anthrax have been those that expose workers to the early stages of the goat hair processing cycle—specifically persons who either sort goat hair or work in the picking, blending, carding, or combing departments. The fine hair from Angora goats which may be contaminated with *B. anthracis* is used to knit sweaters; the contaminated wools are usually the coarser wools used in the preparation of carpet yarn. Hides and skins are processed in the tanning industry for leather goods. Dried animal bones are processed into gelatin, fertilizer, glue, or chemicals. Disease may also develop as a result of laboratory exposure.

EPIDEMIOLOGY

Among the 17 cases of inhalation anthrax reported since 1900, the source of *B. anthracis* in 9 is presumed to have been imported goat hair. Three cases had tanneries as their source; two of these three cases had contact with the same tannery in which imported goat skins were pro-

cessed. One person is presumed to have been infected through contact with imported wool, one with rugs, and one from exposure in a bacteriology laboratory in which *B. anthracis* had been handled. For two persons, the source is unknown, though one, a housewife, lived near a goat hair processing plant and approximately two miles from the tannery mentioned above that been associated with two cases.

In the reported cases in which goat hair was the source of infection, the hair originated in one of several Asian countries in which anthrax was endemic among goats. Hair (or wool) is either pulled from the carcasses of goats that have died of anthrax or is clipped from living animals and becomes infected in the environment either from the soil or as a result of being washed in water with other hair that is already contaminated. Additionally, the mixing of hair from many animals into bales allows contamination to spread to previously noninfected hair. One report associates contamination with the presence of dried animal blood on the hair fibers.

Aerosols generated by processing the contaminated, raw animal fibers are heaviest in the early production stages and result from blending various goat hairs and other animal and synthetic fibers by hand as well as by mechanical agitation of the fibers (8). As the material is processed, the degree of contamination with *B. anthracis* decreases because of the loss of much of the material extraneous to the hair fiber and the continual dilution of goat hair fibers with other animal or synthetic fibers. By the time the thread has been produced, the degree of contamination with *B. anthracis* is very low. The spun thread is then used in weaving the final product, the haircloth interlining. If insulation material, felt, or saddle pads are the final products, the level of contamination with *B. anthracis* is influenced by the dilution of the goat hair fibers with other fibers.

Contamination can be evaluated by bacteriologic examination of the raw or processed materials by using common laboratory materials and culture procedures (2). A culture survey of the environment of a mill—done with saline moistened swabs and floor sweepings—can be useful in demonstrating the degree of environmental contamination (quantitative and qualitative) which usually parallels the contamination level of the animal product being processed in that specific area of the plant. The gradual

decrease in *B. anthracis* contamination of the fiber, and of the environment as the fiber is processed, parallels the gradually decreasing risk of infection with *B. anthracis*.

Only one epidemic of inhalation anthrax has been reported in the United States, and it occurred in 1957 in a goat hair processing mill in Manchester, New Hampshire. A total of nine cases of anthrax resulted; five cases were inhalation anthrax and four of these were fatal (7). The remaining four cases were cutaneous infections. This mill processed goat hair imported primarily from Pakistan. The employees who developed inhalation anthrax worked in carding (2), combing (2), and weaving (1) departments. In order to investigate the levels of airborne contamination that naturally occur in these mills, 91 primates (cynomolgus monkeys) were exposed to the air in a goat hair processing mill similar to the New Hampshire mill (5). The monkeys had a 10%-25% mortality rate caused by inhalation anthrax from a calculated inhaled dose of 1,000-5,500 *B. anthracis* organisms over 3-5 days. Gross and microscopic examination of their tissues revealed findings similar to that for humans who developed inhalation anthrax after industrial exposure to similar *B. anthracis*-containing aerosols.

The predominance of cases associated with goat hair may reflect differences in the degree of contamination in the imported hair as compared to wool or hides, or differences in the methods of processing the raw materials with resulting qualitative or quantitative differences in the derivative aerosols. Variations in exposure risk among various industrial groups may also reflect the number of persons exposed to these materials.

While the majority of cases have occurred in individuals heavily exposed to industrial aerosols, several cases have had minimal exposure. One case was diagnosed in an individual who walked by the open door of the receiving area of a tannery in which contaminated hides were being handled (6). Subsequent to his death, environmental sampling in the receiving area of the tannery demonstrated the presence of *B. anthracis*. It has been hypothesized that as he walked by the tannery, he inhaled an aerosol containing *B. anthracis* that was generated in the receiving area of the tannery. This man had Boeck's sarcoidosis and was on low doses of steroids at the time of his fatal illness. Another

case of inhalation anthrax had been associated with this particular tannery six years earlier.

An unusual case of inhalation anthrax occurred in a home craftsman who was handling imported goat hair yarn which subsequently was shown to be contaminated with *B. anthracis* (14). Evidently, while handling the yarn, he inhaled an infecting dose of *B. anthracis*.

The possibility of subclinical infections has been discussed in a paper describing serologic studies among employees exposed to *B. anthracis* in a goat hair processing mill (11). The authors verified the presence of what was interpreted as significant titers to *B. anthracis* among employees who had no history of a clinical anthrax infection; therefore, they suggested the employees may have had subclinical infections.

POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk includes workers in industries that process imported animal products, including goat hair, wool, hides, skins, and dried bones. The products are imported primarily from Asian, Middle Eastern, and African countries. There are no estimates of the risk of inhalation anthrax alone according to the country of origin of the raw materials or the amount of raw material processed. However, a few studies have been reported describing these associations for cutaneous anthrax alone or cutaneous and inhalation anthrax together. Wolff and Heimann rated imported animals by risk of cutaneous anthrax according to the source (country) of the animal materials (15). They reported that goat hair and skins and carpet wools originating from most parts of Asia and those from Northern Africa and Southern Europe were most likely contaminated with *B. anthracis*. In England, it was estimated that before 1914 about one case of anthrax occurred for every one million pounds of imported East India goat hair processed in English mills (16). There are probably fewer than 5,000 industrial workers currently exposed to these potentially contaminated materials. The number of individuals exposed has been gradually decreasing over the past years because of the increased use of synthetic materials and a reduced demand for goat hair and woolen products. Additionally, improved working conditions and the use of an anthrax vaccine primarily among goat hair workers has also helped reduce the risk of anthrax (4).

Only 17 cases of inhalation anthrax have been reported in the United States since 1900 with 11 of these having occurred since 1955.

PATHOLOGY

Airborne particles of $<5 \mu$ bearing *B. anthracis* are inhaled, passed through the respiratory tract, and deposited in the terminal respiratory alveoli where they are phagocytized by alveolar macrophages and transported across the pulmonary membrane to the hilar and tracheo-bronchial lymph nodes. In this location, the spores germinate, multiply, and produce a potent toxin with resultant toxemia. Bacteremia can develop when bacilli are deposited in multiple organs throughout the body. A characteristic hemorrhagic, edematous, necrotic mediastinitis develops; this may compress the vascular and respiratory structures and cause significant respiratory distress (1). Widespread capillary thrombosis, particularly in the lung and kidney, is an important factor that leads to death. This thrombosis is secondary to endothelial damage produced by the anthrax toxin (9).

CLINICAL DESCRIPTION

Symptoms

The incubation period is from one to five days. The disease is biphasic, with the initial phase consisting of nonspecific symptoms of a mild upper respiratory tract infection, including malaise, myalgia, fatigue, mild fever, nonproductive cough, and, infrequently, a sensation of precordial oppression (12). After two to four days the patient may show signs of improvement. This is followed within 24 to 48 hours by the sudden development of severe respiratory distress with dyspnea, cyanosis, stridor, profuse diaphoresis, and shock. Death usually occurs within 24 hours after onset of the acute phase.

Signs

Physician examination during the initial phase may reveal rhonchi over the lungs without other significant findings. The patient may have a slight fever ranging from 99-100°F. With onset of the acute phase of the disease, temperature, and respiratory and pulse rates all become significantly elevated, and blood pressure falls. It may be possible to demonstrate subcutaneous edema of the chest and neck. Moist, crepitant, pulmonary rales may be heard, and evidence of pleural effusion may be present. Septicemia and

meningitis (frequently hemorrhagic) may occur.

Natural History

Without appropriate therapy, the patient almost invariably dies. Early treatment with large doses of antibiotics and supportive therapy can reverse the natural course of the disease.

Appropriate Laboratory Investigations

During the initial phase no distinctive laboratory findings are present; during the acute phase the white count may increase and show a shift to the left. Radiographic examination of the chest may reveal widening of the mediastinum and the presence of pleural effusion. Under usual circumstances, inhalation anthrax does not present as a primary pneumonia, but secondary anthrax or other bacterial pneumonia may be present. Septicemia may be present. If meningitis complicates the illness, cerebrospinal fluid (CSF) may contain numerous neutrophils ($\geq 12,000/\text{mm}^3$); the protein content will be elevated; and a hemorrhagic component will almost always be present with red blood cell counts $\leq 100,000/\text{mm}^3$. *B. anthracis* is usually demonstrable in the CSF. If pleural fluid is present, it may contain *B. anthracis* organisms.

Treatment

The therapy of inhalation anthrax is based upon empirical knowledge and extrapolation from animal studies. Massive doses of penicillin G by intravenous injection, 50 mg (80,000 units)/kg body weight, as an initial dose given in the first hour, followed by an intravenous maintenance dose of 200 mg (320,000 units) kg/24 h should be used. Streptomycin (7-15 mg/kg body weight/day as a maintenance dose given intravenously to assure adequate blood levels) may also be used. An alternate therapeutic regime is erythromycin 1-4 g/day via continuous intravenous drip. Specific antitoxin has been reported to be of some value; however, currently there is no domestic source of this material. Supportive therapy such as volume expanders, vasopressors, and oxygen should be given as necessary. If there is mechanical respiratory distress, tracheal intubation should be performed. If hospitalized, the patient should be maintained under strict isolation.

Prognosis

Untreated patients do not usually survive; even with treatment, the fatality rate is close to

100%. There has been only one survivor among the 17 reported cases of inhalation anthrax in the American literature since 1900.

DIAGNOSTIC CRITERIA

Inhalation anthrax may be considered in the differential diagnosis of respiratory disease for a person with a history of exposure to possibly contaminated aerosols. The initial phase of the disease is nondescript and can resemble any mild upper respiratory tract infection such as a "cold" or "flu." Unless there is an epidemic, it is doubtful that a diagnosis of inhalation anthrax would be made during the initial phase. The acute phase, with sudden onset and short duration, is characterized by severe toxicity, respiratory distress, and widening of the mediastinum. It may be possible to identify *B. anthracis* in blood, cerebrospinal fluid, or pleural fluid, although these tests may not be of diagnostic help before death.

METHODS OF PREVENTION

The disease in humans could be prevented if the disease in animals were eradicated. Although an effective animal vaccine is available, it is not administered on a regular basis in the countries supplying much of the high-risk animal products. Implementation of improved animal husbandry procedures is difficult to accomplish because of lack of financial and personnel resources; thus, control should be directed toward the worker. Use of the human anthrax vaccine should be mandatory for workers exposed to contaminated materials. The vaccine has been proven to protect against cutaneous anthrax and appears to be equally effective against inhalation anthrax. However, statistical validity has not been demonstrated for protection against inhalation anthrax because of the small number of cases that occurred during the vaccine field trial. Experiments using nonhuman primates have demonstrated the effectiveness of vaccine in preventing inhalation anthrax.

It should be noted that the Occupational Safety and Health Administration (OSHA) has cited at least one company for failure to administer anthrax vaccine to its employees. OSHA recommends the use of the vaccine for employees who have any contact with contaminated animal products.

As demonstrated in England, decontamination of imported raw materials with formaldehyde significantly reduces the risk of anthrax

among employees who work with the animal fibers (13). Additionally, irradiation of contaminated materials has been successfully used in Australia. Also, ethylene oxide has been suggested as an effective decontamination agent.

A meaningful environmental housekeeping program with good control procedures can help reduce the risk of infection. Special attention should be given to an effective ventilation system so that workers are not exposed to contaminated air. Respirators should be worn as this helps reduce the risk of inhaling infective aerosols, but this is not a popular procedure. Workers should be educated about the risk of inhalation anthrax and how to prevent exposure to the organism.

RESEARCH NEEDS

The current methods available for decontaminating raw animal products are expensive and difficult to perform. An easier, less expensive method of decontamination would be advantageous. Patients with fatal inhalation anthrax infection have generalized capillary thrombosis—a phenomenon that should be investigated, and the therapeutic use of anticoagulants or other anticlotting substances should be evaluated. Additionally, the therapeutic use of antitoxin should be evaluated.

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HISTOPLASMOSIS

Jeffrey D. Band

DEFINITION

Histoplasmosis is a systemic fungal infection caused by *Histoplasma capsulatum*, a soil fungus. The organism is almost always acquired by the respiratory route, and the primary focus of infection is in the lungs. In more than 95% of individuals, infection is either inapparent, subclinical, or mild and is usually detected at a later time by x-ray findings of scattered areas of residual pulmonary calcification or the presence of a reactive histoplasmin skin test. In some infected persons, however, a variety of clinical manifestations may result, ranging from overwhelming acute pneumonia to chronic progressive pulmonary disease, or disseminated disease involving many organ systems.

ETIOLOGY

The etiologic agent of histoplasmosis is the dimorphic fungus, *H. capsulatum*. The organism has been found in widespread geographic areas throughout the world. In nature, the fungus exists in a mycelial form which elaborates numerous infectious spores. Once deposited in man, the spores transform into yeast forms.

OCCUPATIONS AND INDUSTRIES IN WHICH EXPOSURE MAY OCCUR

The natural habitat of *H. capsulatum* is the soil (7). It is widely distributed within the temperate zones of the world, but is most heavily concentrated in the central United States. In areas of the Mississippi, Missouri, and Ohio river valleys, more than 90% of all residents have evidence of having been infected with the organism at some time (10). Certain organic nutrients (e.g., fowl and bat excrement), which are found in high concentrations in some areas, favor fungal proliferation (4)(16)(17)(20)(21). In these habitats, the organism grows abundantly where the decaying guano is mixed with soil. Persons whose occupations or other activities involve

close contact with the soil, in particular soil enriched with avian and bat feces, are at high risk of acquiring infection. These include:

- Farmers — especially when cleaning chicken coops, pigeon roosts, and bat-infested lofts.
- Construction workers and workers involved with earth-moving operations.
- Workers involved with road construction, tree clearing, or landscaping.
- Workers involved in the cleaning or dismantling of contaminated buildings.

EPIDEMIOLOGY OF HISTOPLASMOSIS

Certain environmental conditions appear to favor the growth of *H. capsulatum* in soil. Furcolow found that the organism grows best in environments that are warm (mean temperature of 68 to 90 °F), moist (annual precipitation of 35 to 50 inches), and humid (relative humidity of 67% to 87% or more), and that red-yellow podzolic soil and the presence of limestone in soil are associated with the proliferation and isolation of the fungus (9). In addition, soil enriched with high nitrogen content, generally associated with the guano of birds and bats, supports with growth of the fungus.

The distribution of the fungus has been defined by determining histoplasmin skin reactivity in humans and animals in various regions. Numerous investigators have done extensive skin testing in the United States. States along the Mississippi, Ohio, and Missouri river valleys have been shown to be highly endemic and include Arkansas, Kentucky, Missouri, Tennessee, Illinois, Indiana, Ohio, Oklahoma, Alabama, Kansas, Louisiana, Maryland, Mississippi, Texas, and West Virginia (1)(5). Focal areas of high endemicity occur in numerous other states. The infecting agent is an airborne spore. In endemic areas, small numbers of these spores are con-

stantly circulating in the air (10). The chief vector for dissemination of the spores is, therefore, the wind; in dusty weather increased numbers of spores may become airborne and infect individuals. In addition, since higher concentrations of organisms are generally found in areas containing fowl and bat excrement, working, cleaning, or visiting these areas contaminated with avian and bat excrement may lead to the development of infection. A number of outbreaks have been triggered by contaminated dust raised in vigorous cleanup operations of avian or bat feces-laden soil, buildings, or trees. Chicken houses, starling roosts, pigeon roosts, and hollow trees are highly infectious (11)(15) (19). Within specific geographic areas, farm dwellers generally have the largest percentage of histoplasmin positivity, followed by other rural dwellers and lastly city dwellers; however, in some areas nearly everyone is positive.

Histoplasmosis affects all ages and in endemic areas primary infection develops early and equally in both sexes. Disseminated disease tends to occur in the extremes of age, and chronic pulmonary disease usually affects middle-aged men.

Although a wide variety of animals may acquire histoplasmosis, there is no evidence of animal-to-human spread, nor is there evidence of human-to-human spread.

ESTIMATION OF POPULATION AT RISK AND PREVALENCE OF DISEASE

It is difficult to estimate the occupational groups at risk of exposure to *H. capsulatum*. In some areas of the central United States, almost all residents are infected regardless of occupation, and in most cases they are infected during childhood (10). In 4 states the overall percentage of positive skin test reactors for both rural and urban areas exceeds 50%—Arkansas (58%), Kentucky (67%), Missouri (53%), and Tennessee (65%). In the adjacent states of Illinois (73%), Indiana (68%), Ohio (50%), and Oklahoma (60%), more than half of the individuals in farm areas who were tested had positive skin reactions to histoplasmin (1)(5)(6)(12) (13). Previous estimates of the incidence of histoplasmosis in the United States have been as high as 500,000 infections per year (3). Fraser et al. projected that 23.1 persons per 1,000,000 population in the United States are hospitalized each year with histoplasmosis (15,000 persons annually) (8). For

1976, the overall case-fatality rate was 2.9%. Therefore, it has been estimated that approximately 150 persons die from histoplasmosis each year. Based on large skin test surveys, it has been estimated that as many as 15%-20% of Americans have evidence of *H. capsulatum* infection (1)(5)(6)(12)(13)(14).

PATHOLOGY AND PATHOGENESIS

Infection is acquired by inhalation of fungal spores and deposition of the spores in the lungs. Individuals exposed for the first time (primary infection) initially have poor defense mechanisms to fight the infection, and organisms commonly spread via the lymphatic system and blood-stream to distant sites. However, as previously stated, most primary infections result in only mild or unnoticed respiratory infections and are self-limited. Organisms may multiply within reticuloendothelial cells of the liver, lymph nodes, lung, spleen, adrenal glands, intestine, and bone marrow until sufficient numbers and types of inflammatory cells are delivered to contain the organism. The lesions heal by fibrous encapsulation and eventually calcify. Within the nodule, however, the organisms can remain viable but may be held in check by the body's host defenses. In certain clinical settings, the organisms may cause significant pulmonary or systemic disorders later. Successful recovery from the infection confers some immunity against infection.

CLINICAL DESCRIPTION AND DIAGNOSTIC CRITERIA

The signs and symptoms of histoplasmosis range from those of a slight, self-limited infection to fatal disseminated disease, depending upon the quantity of inoculum and certain host factors such as age, prior exposure, and underlying diseases. Infection in healthy persons is usually asymptomatic or presents as a mild febrile respiratory illness. If the exposure is particularly heavy, a more severe influenza-like syndrome or pulmonary infection develops which may or may not be self-limited. Individuals previously exposed to histoplasmosis rarely become ill upon re-exposure unless the inoculum is quite high; even then the respiratory illness is usually less severe and the incubation period shorter than that for previously unexposed individuals. In general the incubation periods, varies from a few days to 3 weeks, depending upon the size of the inoculum and prior exposure. Clinical dissemination rare-

ly occurs except in individuals at the extremes of age or those otherwise immunologically compromised by an underlying malignancy, disorder of the reticuloendothelial system, or corticosteroids or other immunosuppressant therapy. Chronic progressive pulmonary histoplasmosis is uncommon unless significant cavitation occurs or the patient has pre-existing pulmonary disease. Excessive fibrosis of lung tissue and lymph nodes occasionally results in progressive pulmonary disease.

Diagnosis

A firm diagnosis of histoplasmosis is made by either the isolation of the organism from appropriate clinical specimens or the histopathologic demonstration of the organism in tissue specimens. However, the organism rarely can be demonstrated or isolated except in the presence of disseminated disease or chronic pulmonary histoplasmosis. Therefore, indirect clues to the presence of histoplasmosis must be used. These include 1) history of exposure in an endemic area, 2) positive serologic tests, 3) positive skin tests, and 4) development of miliary calcifications in lung and spleen. Unfortunately, serologic and skin tests are sometimes negative for persons with culturally proved histoplasmosis, and test specificity has not been fully established. Numerous other disease entities may resemble histoplasmosis such as the acute nonbacterial pneumonias, hypersensitivity pneumonitis, tuberculosis, brucellosis, sarcoidosis, and lymphoreticular malignancies.

Therapy

Specific anti-fungal therapy for histoplasmosis is indicated for severely ill patients with acute pulmonary histoplasmosis, in patients with disseminated histoplasmosis, or chronic progressive cavitary pulmonary disease. The drug of choice is amphotericin B.

Prognosis

Over 95% of individuals who have been infected with *H. capsulatum* can recall no clinically distinctive illness and remain free of complications of the disease. However, primary acute disease can be serious and indeed fatal. Progressive disseminated disease, untreated, is uniformly fatal. Untreated, the chronic cavitary form of histoplasmosis results in progressive pulmonary disability and death in 50% of affected individuals within 5 years. Primary acute histo-

plasmosis rarely evolves directly into chronic cavitary or disseminated disease.

METHODS OF PREVENTION

Short of avoiding contact with known areas that harbor the organism, prevention of infection is difficult because of its widespread distribution. However, if work needs to be done in areas of known or suspected positivity, prewetting the ground may prevent some airborne dissemination. Only workers who are healthy and have known skin test positivity and normal chest x-rays should engage in the work process, and they should wear protective clothing and masks. Chemical decontamination with 3% formaldehyde has been shown to be an effective short-term fungicidal agent and may be useful, in addition to wetting the ground before work, in preventing outbreaks among workers (18)(22). There is no effective vaccine to prevent histoplasmosis.

RESEARCH NEEDS

Additional study is needed on the chemical, physical, and biologic factors influencing the growth of *H. capsulatum* in soil. Improved means of controlling large aggregations of birds and roosts should be sought. Safer and easier methods to decontaminate soil or other contaminated foci should be explored. Further work is necessary to develop an effective and safe vaccine to prevent disease in individuals at high risk for developing complications of the disease. Lastly, improvement is needed in the serologic diagnosis of histoplasmosis, and other less toxic agents for treatment need to be developed.

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BRUCELLOSIS

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DEFINITION

Brucellosis is an infectious disease caused by microorganisms of the genus *Brucella*. It usually affects domestic animals but can be transmitted to humans. Domestic animal diseases that are of public health concern are caused by *Brucella abortus*, *Br. suis*, and *Br. melitensis*. *Br. abortus* most commonly infects cattle, causing abortion late in pregnancy and a subsequent high infertility rate. Brucellosis in swine is most often caused by *Br. suis* and is a chronic disease manifested by sterility or abortion in sows, high piglet mortality rates, and orchitis in boars. *Br. melitensis* is the most common cause of brucellosis in goats, causing abortion late in pregnancy. *Br. canis*, affecting mainly dogs, has been associated with only a limited number of human infections and appears to be a less important human public health concern than the other three species.

Brucellosis in humans can be caused by any of the *Brucella* species and is an illness characterized by fever, chills, sweating, malaise, weakness, headache, myalgia, anorexia, and loss of weight.

ETIOLOGY

The etiological agents of Brucellosis are *Brucella abortus*, *Br. suis* and *Br. melitensis*. These *Brucella* microorganisms are pleomorphic, short, and slender coccobacilli. They stain gram-negative; bipolar staining is sometimes present. Differential characteristics of *Brucella* species based on physiological requirements and gas formation, growth in the presence of dyes, oxidative metabolic activities, lysis by phagocytes, and agglutination in monospecific antisera help identify individual species. No exotoxins are formed, but the cell has enterobacterial endotoxins.

OCCUPATIONS AND INDUSTRIES INVOLVED

As an occupational disease, brucellosis occurs in livestock producers, veterinarians, and rendering plant and abattoir employees. The incidence of the disease in the United States is steadily declining, with only about 200 cases currently being reported annually. Approximately half of the cases, primarily those in abattoir workers, are acquired from exposure in an industrial setting (Table IX-1)(5).

EPIDEMIOLOGY

In the United States, the reported incidence of brucellosis has declined from a peak of 6,321 cases in 1947 to its current plateau of 200 cases per year. Pasteurizing dairy products and attempting to eradicate the disease from livestock have been primarily responsible for the falling incidence of human brucellosis. Proportionately more abattoir employees than members of the general population continue to acquire brucellosis; of 2,126 cases from 1968 to 1977 for which information was available, 1,215 (57%) were in abattoir workers.

One investigation of brucellosis infection rates and route of infection in a swine abattoir (EPI 74-2-3, consultation on abattoir-associated brucellosis, Smithfield, Virginia, issued March 1974) revealed a 9% rate of seropositivity, and a greater correlation between exposure to airborne organisms in air from the kill department (Figure IX-1) than to conjunctival or skin contact with hog tissues or tissue fluids. Employees engaged in slaughtering and processing operations performed before deep tissues were exposed (Stage I Operations); in processing operations involving exposure to fresh raw tissue (Stage II Operations); or in other tasks requiring prolonged

Table IX-1
MOST PROBABLE SOURCE OF BRUCELLOSIS
BY OCCUPATIONAL GROUP OF PATIENTS, UNITED STATES, 1965-1974

	Occupational Group			Total
	Meat-Processing Industry	Livestock Industry	Other and Unknown	
<i>Source</i>				
<i>Domestic Animals</i>				
Swine	702	54	39	795
Cattle	121	179	52	352
Swine or Cattle	186	60	45	291
Sheep or Goats	7	5	6	18
Unspecified Farm Animals	57	4	2	63
Dogs	0	0	6	6
<i>Wild Animals</i>				
Caribou or Moose	0	0	12	12
Feral Swine	0	0	7	7
Deer	0	0	2	2
<i>Unpasteurized Dairy Products</i>				
Domestic	0	7	57	64
Foreign	0	2	125	127
<i>Accidents</i>				
Strain 19 vaccine	0	31	0	31
Laboratory	0	0	34	34
<i>Unknown</i>				
	0	12	233	245
Total	1,073	354	620	2,047
Percentage of Total	52.4	17.3	30.3	

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exposure to the kill department (Mixed Operations), had the highest rates of seropositivity (Table IX-2).

In their review, Buchanan et al. noted all the major outbreaks of brucellosis that occurred in the period 1960-1972 were associated with swine slaughter (3). However, a resurgence of bovine brucellosis beginning in 1971-1972 made cattle the primary source of abattoir-acquired brucellosis by 1976.

POPULATION AT RISK

Of abattoir employees, kill department workers are at greatest risk of acquiring brucellosis. Although kill department workers constitute less than 20% of the approximately 150,000

abattoir workers in the United States, those with kill floor exposure have approximately 75% of the *Brucella* infections reported for abattoir employees. The multiple types of exposure to potentially contaminated animal tissues experienced by most kill department workers prevent the identification of the single "most" significant route.

PATHOLOGY

After they invade the body, brucellae localize in the bone marrow, lymph nodes, liver, and spleen. There they induce reticuloendothelial hyperplasia and the formation of small miliary granulomata. These have many similarities to the granulomata of sarcoidosis and miliary tubercu-

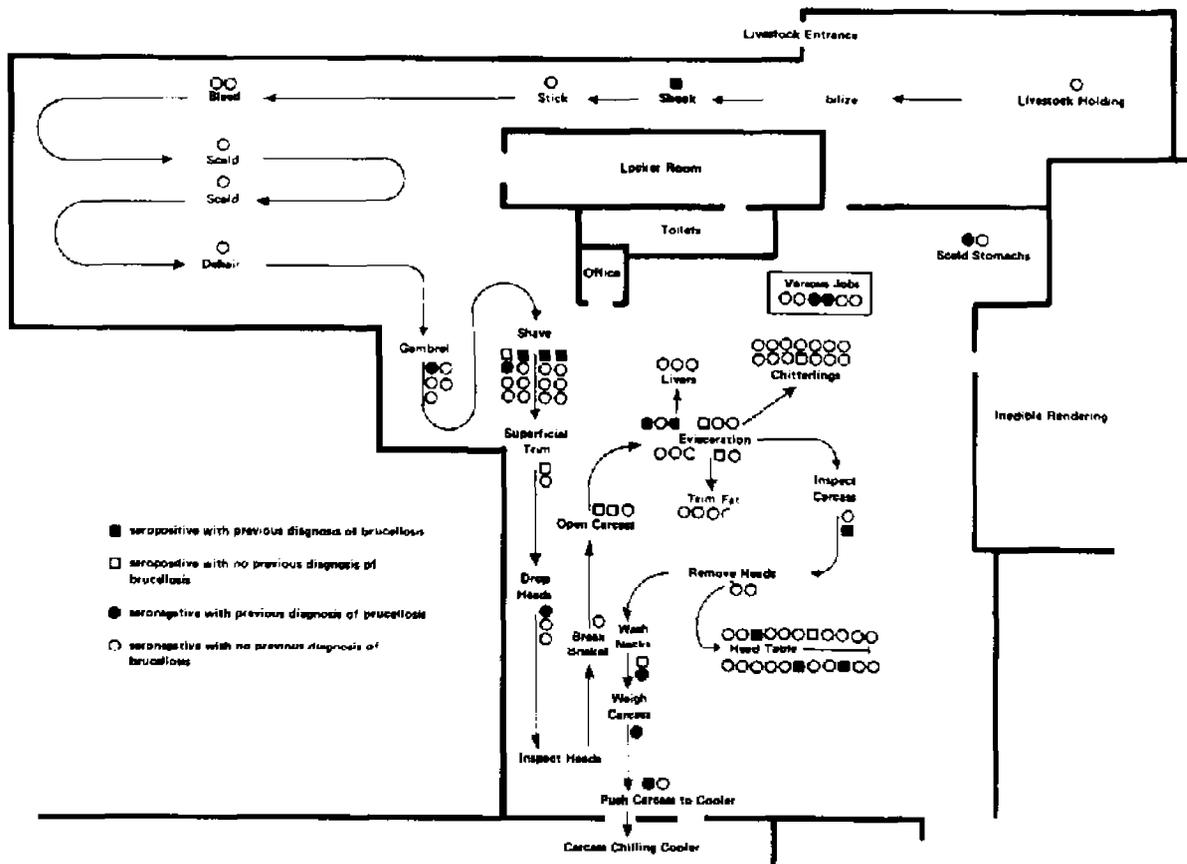


Figure IX-1. Hog Kill Department Employees by Work Location, *Brucella* Seropositivity and Previous History of Brucellosis, Smithfield, Virginia Packing Plant.

losis and consist of collections of macrophages and reticuloendothelial cells surrounded by a zone of mononuclear cells with some fibroblasts. Often there are giant cells. Rarely the center of the lesion may undergo necrosis with an associated polymorph infiltration, but typical caseation as seen in tuberculosis does not occur.

CLINICAL DESCRIPTION

Commonly reported symptoms of brucellosis include malaise, chills, sweating, weakness, body aches, headache, and anorexia. Clinical signs seen at physical examination include fever (either constant or intermittent), lymphadenopathy, and splenomegaly. Untreated, the illness may last for many months and can cause complications such as spondylitis, osteomyelitis, or endocarditis. Even with antibiotic therapy the patient may be ill for a month or more. Brucellosis is rarely fatal.

The treatment of choice for humans with brucellosis is tetracycline, 2 g daily by mouth for 21 days, with or without streptomycin, 1 g daily intramuscularly for 14 days. Buchanan et al.

observed that patients treated with tetracycline and streptomycin had a lower rate of relapse than those treated with tetracycline alone or in combination with other drugs (2).

DIAGNOSTIC CRITERIA

Brucellosis can be definitively diagnosed by isolating the causative organism in culture. Blood is added to tryptase broth and incubated in an atmosphere containing 25% CO₂. The enrichment culture should be subcultured at four-day intervals and, if subcultures are negative, carried for a period of not less than three weeks. For subculture, agar plates of liver infusion or tryptase agar should be inoculated. Individuals suspected of being infected by *Brucella* microorganisms should have appropriate blood samples taken from cultures. Attempts to isolate the organism should be repeated several times before therapy is instituted since bacteremia may be intermittent. For patients with chronic brucellosis, cultures of blood, bone marrow, and other tissues may be productive.

Table IX-2
SEROPOSITIVITY BY WORK DEPARTMENT
SMITHFIELD, VIRGINIA — SEPTEMBER 1973

	Centrifugation Agglutination Test Titer>1:160			
	All Employees Surveyed		Excluding Employees in Departments Other Than Kill Who Previously Worked in the Kill Department	
<i>Stage I Operation</i>				
Kill Dept.	6/31	(19.4%)	6/31	(19.4%)
<i>Stage II Operations</i>				
Kill Dept.	11/81	(13.6%)	11/81	(13.6%)
Lard Rendering Dept.	2/7	(28.6%)	2/6	(33.3%)
Inedible Rendering Dept.	0/8	(0.0%)	0/8	(0.0%)
Total Stage II	13/96	(13.5%)	13/95	(13.7%)
<i>Stage III Operations</i>				
Cut Dept.	4/51	(7.8%)	4/41	(9.8%)
Conversion Dept.	0/5	(0.8%)	0/3	(0.0%)
Ham Boning Dept.	0/19	(0.0%)	0/14	(0.0%)
Bacon Slicing Dept.	0/21	(0.0%)	0/18	(0.0%)
Cure-Pump-Hang Dept.	0/11	(0.0%)	0/10	(0.0%)
Smoked Meat Packing Dept.	2/17	(11.8%)	0/14	(0.0%)
Sausage Packing Dept.	0/19	(0.0%)	0/14	(0.0%)
Sausage Chopping Dept.	0/4	(0.0%)	0/4	(0.0%)
Sausage Stuffing Dept.	0/6	(0.0%)	0/5	(0.0%)
Fresh Sausage Dept.	1/14	(7.1%)	0/10	(0.0%)
Total Stage III	7/167	(4.2%)	4/133	(3.0%)
<i>Mixed Operations</i>				
Maintenance Dept.	5/24	(20.8%)	3/20	(15.0%)
Miscellaneous Dept.	2/11	(18.2%)	1/7	(14.3%)
Total Mixed	7/35	(20.0%)	4/27	(14.8%)
<i>NonProcessing Operations</i>				
Delivery Dept.	0/28	(0.0%)	0/28	(0.0%)
Sanitation Dept.	0/4	(0.0%)	0/3	(0.0%)
Total NonProcessing	0/32	(0.0%)	0/31	(0.0%)
GRAND TOTAL	33/361	(9.1%)	27/317	(8.5%)

Brucellosis is commonly diagnosed serologically. The standard tube agglutination (STA) test is the most sensitive and widely used serologic test in the United States. Although this procedure involves using *Br. abortus* as antigen, it can be used to detect infections caused by *Br. melitensis*, and *Br. suis*, because all three have common antigenic determinants. *Br. canis* infection, however, can only be detected by using the specific antigen.

The 2-mercaptoethanol (2-ME) degradation test is used as an adjunct to the STA test. 2-ME, added to patient's serum before an agglutination test is performed, dissociates the IgM molecules so that any residual agglutination is caused by IgG antibodies. It has been found that the level of IgG remains elevated in persons with chronic brucellosis and disappears in those who are adequately treated. Thus the 2-ME test is particularly useful when low STA titers could indicate either current or past infection.

Both cholera vaccination and tularemia can falsely elevate STA titers (usually only minimally). The etiology of the elevated STA titer can be resolved by evaluating a clinical history or results of specific serological absorption studies.

Individuals suspected of having brucellosis, but whose culture and serologic results are negative pose a significant diagnostic problem. Of the several possible reasons for negative serologic results, the most important are 1) the prozone phenomenon, 2) the presence of blocking antibody in patient serum, 3) *Br. canis* infection in an individual whose sample was analyzed with an STA test in which *Br. canis* was not used as antigen, and 4) the disease is not brucellosis.

The problems of the prozone phenomenon and blocking antibody can be countered with specialized serologic techniques. Since prozone occurs only at lower serum dilutions, serial dilutions of serum samples should all be evaluated before the test is reported to be negative.

The presence of a blocking antibody is more difficult to prove than the prozone phenomenon, but it can be documented by using the Coombs test or centrifuging the reaction tubes before incubation.

PREVENTION

Although eye and skin protection should lower the risk of industrially related brucellosis, protective clothing and equipment commonly worn in abattoirs have apparently not been very

effective. Metal mesh gloves protect against more serious cuts, but minor scratches and abrasions provide equally effective portals of entry for *Brucella* organisms. Rubber gloves should provide protection against contact exposure, but the gloves generally used do not cover wrists and forearms, and blood and other potentially infectious materials can enter the gloves through their open end and through accidental perforations. Where the conjunctival route of infection is important, ordinary eyeglasses have not been shown to provide protection.

Other than reducing unnecessary exposure to potentially infectious aerosols generated in the kill room, little can be done on a practical basis to prevent airborne or other transmission of brucellosis to abattoir workers. However, early diagnosis and appropriate therapy will reduce the duration and severity of the illness as well as the frequency of complications.

Only essential personnel should enter the kill room, which should be under negative air pressure in relation to other work areas. Employees should be instructed on how brucellosis is acquired, its symptoms, and the need for prompt diagnosis and therapy. Brucellosis should be routinely considered in the differential diagnosis of febrile illnesses in abattoir workers.

RESEARCH NEEDS

Surveillance of brucellosis and the epidemiologic study of specific problems dealing with abattoir-associated brucellosis should be continued. This is especially important where recommended control measures are of potential rather than proven benefit. Efforts to develop a safe and effective human brucellosis vaccine need to be continued, and vaccine use would probably be highly cost beneficial when administered to targeted populations such as abattoir or laboratory workers.

Further clinical studies dealing with safe and effective treatment of brucellosis are needed. New antibiotics such as trimethoprim-sulfonamide combinations must be thoroughly evaluated before they can be confidently recommended for treating patients with brucellosis.

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TUBERCULOSIS AS AN OCCUPATIONAL DISEASE

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DEFINITION

Tuberculosis is a communicable disease of man and animals caused by the bacterium *Mycobacterium tuberculosis* and, less frequently, *M. bovis*. Lesions most often occur in the lungs but may be found in any part of the body.

CAUSATIVE AGENTS

Species of *Mycobacterium* are characterized by unusual "acid fast" staining properties, slow growth, relative resistance to chemical disinfectants, and the ability to survive for decades within cells in the infected animal. Several species are known to cause human illness, but the virulence and communicability of *M. tuberculosis* make it by far the most significant human pathogen. With the exception of a comment in Research Needs, the information in this section pertains to *M. tuberculosis*.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

Tuberculosis is a contagious disease and can spread among individuals of any occupation. The few published studies of tuberculosis as an occupational hazard suggest that physicians, nurses, medical laboratory workers, and miners are at increased risk of tuberculosis (1)(3)(4). Other occupations presumably at increased risk are migrant workers, overseas personnel in any occupation, zoo employees, prison guards, and social workers and others who work with the impoverished and the derelict.

EPIDEMIOLOGY

Infection is almost always acquired via inhalation of contaminated microscopic particles generated by coughing, sneezing, speaking, or singing. Therefore, persons most likely to become infected are those with a prolonged exposure in a confined area to an infectious person.

In 1981, 27,373 cases of tuberculosis were reported in the United States for an annual incidence of 11.9 per 100,000 persons. The incidence is higher in older age groups, in nonwhite persons, and in males. The incidence is also high among immigrants, alcoholics, and prisoners, but sufficient data are not available to calculate specific rates.

Unfortunately, few studies of tuberculosis incidence among various occupations have been reported. Therefore, only general and somewhat unsatisfactory comments can be made about tuberculosis as an occupational hazard.

Doctors, nurses, and medical laboratory workers are at greater risk than the population as a whole because they care for persons with tuberculosis. Barrett-Connor recently estimated the infection rate of physicians was about twice that of the general population (1). Harrington calculated the disease rate of medical laboratory workers in England was above five times that of the general population (see Table IX-3) (3). Individuals who work with elderly persons, nonwhite persons, immigrants, alcoholics, or prisoners presumably are at increased (but unquantitated) risk of infection.

Miners and others who work in poorly ventilated areas are more likely to be infected by a fellow worker who has tuberculosis than are persons who work in well ventilated areas. Studies among different groups of miners show that the tuberculosis mortality rate ranges from approximately 1.5 times expected for coal miners to approximately 10 times expected for cummingtonite-grunerite miners (see Table IX-3)(4)(5).

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

Table IX-3 shows that between 1,099 and 4,784 persons have tuberculosis disease because they work in a medical or mining occupation. Un-

Table IX-3
ESTIMATED NUMBER OF PERSONS WITH TUBERCULOSIS
ATTRIBUTABLE TO OCCUPATIONAL EXPOSURE, 1977

Occupation	Number of Persons (1)	Relative Risk of Tuberculosis	Estimated Incidence (4)	Estimated Attributable Incidence	Estimated Prevalence (5)	Estimated Attributable Prevalence
Medicine	3,853,000	2-5(2)	1,071-2,678	536-2,142	2,142-5,356	1,071-4,284
Mining	200,000	1½-10(3)	42-278	14-250	84-556	28-500
Social Workers	444,000					
Prison Guards						
Zoo employees						
Migrant Workers	130,000					
Overseas employees						

(1) U.S. Bureau of Census, 1978.

(2) Barrett-Conner, 1979; Harrington 1976.

(3) McDonald, 1978; Rockette, 1977.

(4) Based on United States incidence in 1977 of 13.9 per 100,000.

(5) Assumes average duration of illness is 2 years.

fortunately, sufficient data are not available to estimate the risk to persons in other occupations.

PATHOLOGY

Most tuberculous infections follow inhalation of the bacteria. Less frequently, infections occur after ingestion of direct inoculation through the skin. The bacilli multiply at the site of initial implantation and, if not contained by host defenses, are carried through the lymphatics to local and then more distant lymph nodes.

Usually the bacilli are contained by the host defenses. In some cases, however, either shortly after infection or after a prolonged dormancy, the organisms continue to multiply causing the systemic signs and symptoms of chronic infection with progressive destruction of the organ primarily involved (most often the lungs).

Workers exposed to silica are more likely to have tuberculosis because silica interferes with the function of the pulmonary macrophages (6). We do not know if other chemicals or minerals predispose to tuberculosis for similar reasons.

CLINICAL DESCRIPTION

Symptoms

Pulmonary tuberculosis is manifested by constitutional symptoms of loss of appetite, weight loss, fatigue, fever, night sweats, malaise, and organ-specific symptoms of cough (often productive of sputum and/or blood) and chest pain. Tuberculosis of other organs (such as kidneys or bones) causes the constitutional symp-

toms listed above plus symptoms specific to the organ involved.

Signs

Pulmonary tuberculosis, depending on its severity and duration, may be associated with nonspecific signs of chronic infection such as anemia. Pulmonary tuberculosis also may produce a variety of signs related to the respiratory tract such as rapid breathing and abnormal physical signs on percussion and auscultation of the chest. The chest x-ray is usually abnormal and often characteristic, but never diagnostic of tuberculosis. The lesions are usually patchy, in the apices of the lungs, and often cavitory.

The signs of tuberculosis of other organs include the (already mentioned) nonspecific signs plus signs specific to the organ involved. For example, tuberculous meningitis may cause cranial nerve damage, blindness, deafness, and disorders of consciousness from confusion to coma. Examination of the cerebral spinal fluid usually shows an increased cell count, increased protein concentration, and decreased glucose concentration. *Mycobacterium tuberculosis* may be demonstrated by appropriate stain or culture.

The Natural History of Disease

Most infections with *M. tuberculosis* are subclinical or unrecognized; the only evidence of infection is a positive tuberculin skin test. Progressive disease occurs in about 5% of persons within the first year after infection and in another 5% later in life. Therefore, once in-

ected, the risk of progressive disease exists for life. Unless treated with antituberculous chemotherapy, about 50% of persons who develop clinical illness die, frequently after months to years of progressive debilitation. Modern chemotherapy, however, if administered promptly and properly (see Treatment), will cure most patients.

Appropriate Laboratory Studies

The single most important laboratory study is the examination of secretions—usually sputum — or tissue for the infecting organism. Special media and procedures are required to culture *M. tuberculosis*. For persons with pulmonary tuberculosis, chest x-ray also is important.

Treatment

Antimicrobial drugs can cure tuberculosis. However the capability of the slowly growing *M. tuberculosis* to lie dormant within the host's cells necessitates prolonged drug treatment. Currently recommended therapy is 9-18 months of daily treatment with 2 or more drugs. Prolonged bed-rest and surgery, formerly the mainstays of therapy, now have a very limited role in the treatment of tuberculosis.

Prognosis

Promptly and properly administered chemotherapy confers an excellent prognosis. Although treatment is prolonged, most patients recover with minimal residua. Unfortunately, the long duration of treatment often results in erratic or incomplete ingestion of medicines. Inadequate chemotherapy may result in recurrent episodes of disease, progressive disability, and death.

DIAGNOSTIC CRITERIA

The diagnosis of tuberculosis is confirmed by the growth of *M. tuberculosis* from culture of sputum, CSF, urine, lymph nodes, or other infected tissue. If the organism cannot be grown, the diagnosis of tuberculosis should be made if the patient has a positive tuberculin skin test, the signs and symptoms are compatible with tuberculosis, a thorough evaluation uncovers no other cause for the illness, and the response to therapy is appropriate.

The most common diseases mimicking tuberculosis are systemic fungal infections, other mycobacterial infections, sarcoidosis, cancer, and the pneumoconioses.

METHODS OF PREVENTION

Transmission of tuberculosis can be prevented by the rapid identification and treatment of persons with disease and by the identification and treatment of those persons infected but not yet diseased (i.e., persons with only a positive skin test).

RESEARCH NEEDS

1. More information is needed about the incidence of tuberculosis in occupational groups, particularly those presumed to be at risk of infection.
2. Although a synergism between silicosis and tuberculosis is established, little information exists about possible synergism between tuberculosis and other mineral and chemical exposures.
3. The probable salubrious effect of more active participation of employers in the maintenance of chemotherapy among infected employees should be explored. Patients with tuberculosis can work and the workplace may be a good place to encourage regular drug usage to prevent relapse, progressive disease, and possible transmission. (Denial of employment to a noninfectious person who is on medication, because of fear of spread to fellow employees, is counter-productive and should not be tolerated.)
4. Cost-effective methods to identify contagious persons earlier in the course of illness need imaginative research.
5. Information is needed about the incidence of other Mycobacterial infections among various occupational groups.

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PSITTACOSIS

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DEFINITION

Psittacosis is an acute infectious disease of humans characterized by fever, pneumonia, cough, weakness, fatigue, chills, headaches, myalgia, and occasionally myocarditis and encephalitis.

ETIOLOGIC AGENT

The etiologic agent, *Chlamydia psittaci* is one of several microorganisms that comprise the single genus *Chlamydia*. Once considered to be viruses because they reproduced only within host cells, several properties clearly relate *chlamydia* to bacteria: 1) the presence of both DNA and RNA, 2) division by binary fission, 3) cell walls like those of free-living gram negative bacteria, and 4) susceptibility to antibiotics. *Chlamydia psittaci*, has its reservoir in various domestic and wild birds. The disease has been called psittacosis when it affects psittacine species (i.e., parrots and related birds) and ornithosis when it affects other avian species. Although these terms have been used interchangeably, perhaps the more general term "chlamydiosis" would be preferable.

OCCUPATIONS AND INDUSTRIES INVOLVED

Psittacosis is an occupational health hazard for a large and growing number of individuals employed in quarantine facilities, pet shops, breeding aviaries, veterinary clinics, diagnostic laboratories, and avian distribution networks including wholesale aviaries and air or surface freight companies. Psittacosis (ornithosis) in turkey flocks causes many sporadic human cases in the poultry processing industry. The total number of persons at risk of occupationally related psittacosis is uncertain but probably exceeds 20,000. Approximately 70 cases of psittacosis have been reported annually in the past decade, with about one-third being occupation-

ally acquired or associated. In the period 1975-1977, 48 (20%) of 236 reported cases were associated with the patients' occupations: 22 with the pet bird industry and 26 with the poultry processing industry (Table IX-4) (2).

EPIDEMIOLOGY

Although psittacosis was rarely reported in the United States before 1929, in November of that year, cases of psittacosis began to be reported from various sections of the country. Within the next 6 months, nearly 200 cases (33 fatal) of psittacosis were reported. After these cases were shown to be associated with exposure to parrots imported for the 1929 Christmas trade, the commercial importation of parrots was prohibited in January 1930. Investigations in the period 1935-1950 revealed that psittacosis affected many or all avian species. When available effective antibiotic therapy had lowered the mortality rate, restrictions on importation and interstate shipment of psittacine birds were relaxed. Currently, psittacine birds are imported into domestically located quarantine stations supervised by the U.S. Department of Agriculture (USDA). Although the quarantined birds must be treated with chlortetracycline, adequate blood levels of antibiotics are not always achieved, as evidenced by the fact that psittacosis has been diagnosed in psittacine birds recently released from quarantine. Some employees and government inspectors at quarantine facilities have also had psittacosis.

In the past decade, 8 epidemics involving 142 cases have occurred at 7 turkey processing plants in Texas, Missouri, and Nebraska (Figure IX-2). In an investigation of one outbreak, inhalation of infectious aerosols was clearly implicated as the primary route of exposure (1). Employees in the kill and pick evisceration departments were at the greatest risk.

Although direct contact or inhalation of

Table IX-4
HUMAN PSITTACOSIS CASES BY TYPE OF EXPOSURE
AND MOST PROBABLE SOURCE OF INFECTION, UNITED STATES, 1975-1977

<i>SOURCE</i>	<i>Non-Bird Owner</i>	<i>Pet Bird Owner</i>	<i>Bird Fancier</i>	<i>Pigeon Fancier</i>	<i>Pet Shop Employee</i>	<i>Other Commercial Trade</i>	<i>Poultry Production</i>	<i>Poultry Processing</i>	<i>Miscellaneous</i>	<i>Unknown</i>	<i>Total</i>	<i>Percentage of Total</i>
Budgerigars	2	28	3			1			1	1	36	15.2
Cockatiels	1	12	1								14	5.9
Other Psittacine sp.	3	19	3		7	1					33	14.0
Unspecified Psittacine sp.	3	3	2		5	2					15	6.4
Psittacine/Non-Psittacine	3	6	6		6				2		23	9.7
Canaries/Finches	1	3									4	1.7
Domestic Pigeons	4	1	1	17						1	24	10.2
Wild Pigeons	7	2							4	2	15	6.4
Miscellaneous Wild Birds	3	1									4	1.7
Turkeys							1	26	2		29	12.3
Chickens	1						3				4	1.7
Turkeys/Other Birds							1		1		2	0.8
Other Miscellaneous	4	1							2		7	3.0
Unknown										15	26	11.0
Total	43	76	16	17	18	4	5	26	12	19	236	100.0

aerosolized tissues has been implicated in disease transmission in turkey processing plants, infection can also be spread by aerosolized bird feces. Person-to-person transmission has been reported only rarely and probably is not important in the epidemiology of the disease.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

See Table IX-4 above.

PATHOLOGY

Postmortem examination of persons who have died from psittacosis generally reveals focal or lobar consolidation of the lungs. The alveoli may be filled with exudate and alveolar septal cell hyperplasia may be marked; bronchioles are

rarely involved. Splenomegaly is common, and normal splenic architecture may be altered by reticuloendotheliale hyperplasia and focal necrosis. Hepatic focal necrosis is also common. Cardiac involvement in psittacosis cases has been associated with hemorrhagic areas in the endocardium of the valves and evidence of pericarditis and myocarditis.

CLINICAL DESCRIPTION

Although psittacosis is primarily a respiratory disease, it can cause a wide variety of clinical manifestations. Generally, about 10 days (range 4 to 15 or more days) after infection occurs, the clinical illness begins abruptly with fever, chills, weakness, fatigue, myalgia, anorexia, nausea, vomiting, diaphoresis, dyspnea, headache, back-

PSITTACOSIS IN HUMANS, UNITED STATES, 1965-1977

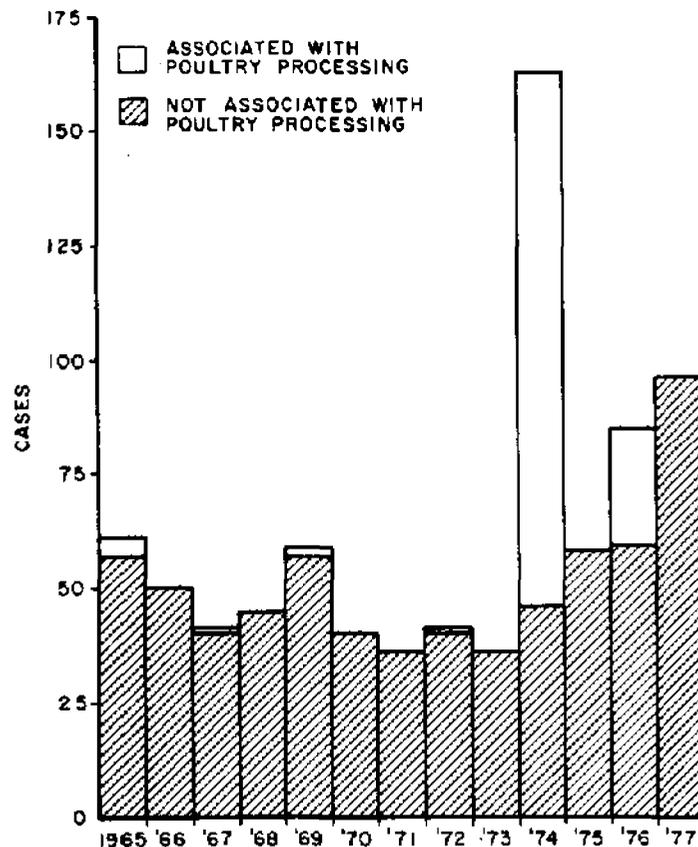


Figure IX-2. Psittacosis in humans, United States, 1965-1977

ache, and photophobia. Prominent clinical signs include pneumonia, weight loss, pleuritic chest pain, hepatomegaly, splenomegaly, and meningismus. Other than a nonproductive cough, signs and symptoms of pneumonia are often minimal, however, chest x-rays commonly reveal a surprising degree of pulmonary involvement. The patchy infiltrates caused by psittacosis frequently resemble those caused by a number of viral agents.

Psittacosis is a systemic disease and can involve multiple organs. Hepatitis, endocarditis, myocarditis, thrombophlebitis, meningoencephalitis, pericardial effusion, disseminated intravascular coagulation, and myositis have all been reported.

Tetracyclines are the drug of choice for treating patients with psittacosis. Chloramphenicol, erythromycin, gentamicin, penicillin, and

ampicillin have also been used, but reports of their therapeutic efficacy are largely anecdotal. The dosage and duration for adequate tetracycline therapy are still in dispute. Some authorities recommend 2 grams daily by mouth for 7 days after defervescence (5); others recommend 1 gram daily by mouth for 21 days (7). Most authorities agree that inadequate therapy leads to a risk of relapse.

Although there is generally a dramatic response to tetracycline, the patient may continue to tire easily even after adequate therapy. The case-fatality rate of reported cases in the United States is approximately 1%.

DIAGNOSTIC CRITERIA

A diagnosis of psittacosis is based upon a history of exposure to birds, evidence of infection in the suspected avian source, signs and

symptoms, and laboratory findings.

The laboratory diagnosis of psittacosis relies on serologic test results or cultural isolation of *Chlamydia psittaci*. If possible, the etiologic agent should be isolated before antibiotics are given. Clinical specimens for culture include blood clots and throat washings, which should be shipped to the laboratory frozen on dry ice. Commonly used test systems involve inoculating patient specimens into tissue culture, mice, and eggs. Typical inclusions are then demonstrated with the Gimenez modification of Macchiavello's technique. Laboratory personnel should take special precautions in handling *Chlamydia psittaci* specimens; they are highly infectious.

The complement fixation test is the most widely used serologic procedure for diagnosing psittacosis. A fourfold change in titer (to at least 32) between 2 serum samples collected 2 or more weeks apart, and tested concurrently, is generally accepted as evidence of current infection. Inasmuch as a chlamydial group antigen is used in the serologic test for psittacosis, a history of other chlamydial infections such as lymphogranuloma venereum must be taken into account when results are interpreted.

PREVENTION

No effective vaccine has been developed for psittacosis. Whether naturally acquired infection confers immunity to humans is still not known; infected birds do not become immune.

Controlling exposure to psittacosis for employees in the pet bird trade would probably require banning the importation of psittacine birds, or tightly controlling individual bird identification, importation, and interstate shipment. Adequate controls may not be cost effective. The USDA has intermittently sponsored a program of screening and tetracycline treatment of turkeys to be slaughtered—in attempts to minimize the public health problem associated with poultry processing.

RESEARCH NEEDS

Improved techniques for the treatment of psittacosis in infected birds are needed because currently recommended tetracycline feeding procedures are not reliable. In the case of psittacine birds other than parakeets, the procedures are complicated and may cause adverse side effects in the birds.

Serologic methods with a high degree of sensitivity and specificity are needed for accurate

diagnosis. Current complement fixation tests do not clearly differentiate psittacosis from other human chlamydial infections. Other chlamydial diseases are more common than psittacosis, and preexistent antibodies due to these diseases may lead to misdiagnosis of respiratory diseases due to nonchlamydial organisms such as psittacosis. In addition, the clinical spectrum of the various chlamydial diseases overlap, further complicating accurate diagnosis.

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SECTION X
HEART DISEASE—COR PULMONALE



HEART DISEASE, COR PULMONALE

Richard L. Naeye

INTRODUCTION INCLUDING DEFINITIONS

Cor pulmonale is defined as heart failure caused by lung disease. The right ventricle of the heart malfunctions due to pulmonary arterial hypertension. Increased pulmonary vascular resistance resulting in pulmonary arterial hypertension may be caused by anatomic or vasomotor narrowing of small arteries and arterioles or both. A variety of occupational agents can produce pulmonary vascular abnormalities and cor pulmonale. Each will be considered. Despite their variety, there are only a limited number of ways in which pulmonary blood vessels can react to noxious stimuli. Knowledge of these response patterns will explicate cor pulmonale in individual occupational disorders—particularly its diagnosis, clinical features, reversibility, and prevention.

There may be important interactions between occupational and nonoccupational agents that affect pulmonary vessels. These interactions will be discussed together with genetic factors that likely affect pulmonary vascular resistance in occupational lung disease. Pulmonary vascular abnormalities in occupational lung disease usually affect the heart by increasing the pressure load on the right ventricle. Factors that may affect the reaction of the heart to this pressure load are also to be considered.

In adults, about half of normal pulmonary vascular resistance is located in the pulmonary arteries, one third in the capillaries, and the remainder in the pulmonary veins (5). This differs from systemic circulation distribution where most of the resistance lies in the arterioles. Before birth, both circulations have arterioles. Muscle normally disappears from the arterioles in the pulmonary circulation within two weeks of birth, markedly decreasing its resistance. Lacking arterioles, blood flow cannot be as finely controlled in the lung as in the systemic circulation.

Autonomic nervous system regulation of blood flow, so important in the systemic circulation, is almost absent in the pulmonary circuit. Many drugs that affect systemic vascular resistance have almost no influence on pulmonary vascular resistance.

Arteriolar disease is the principal cause of increased resistance and hypertension in the systemic circulation. Since the pulmonary circuit lacks arterioles, it might be assumed that increased resistance and hypertension would be rare in the lesser circuit. Such is not the case. The pulmonary blood vessels are in much closer proximity to the external environment than are their systemic vascular counterparts. As a result, environmental agents more frequently damage pulmonary than systemic blood vessels. Many of these agents are in the daily work environment and are thus the cause of occupationally induced pulmonary arterial hypertension and cor pulmonale.

In some respects, the cardiac right ventricle is less suited to respond to pressure load increases than is the left ventricle. By 6-8 years of age, the two ventricles no longer respond to increased workloads with myocardial fiber hyperplasia. From that age, hypertrophy is the main response. Hypertrophy is more limited as a response mechanism to pressure loads than is hyperplasia because fiber surfaces available for nutrient and gas exchange are relatively decreased with fiber hypertrophy; they are not much challenged by hyperplasia. Hypertrophy effectively limits the size which individual myocardial fibers can reach without metabolic impairment. Occupationally induced pulmonary arterial hypertension develops at an age when the heart can only respond to increased loads with hypertrophy. Resultant pressure workload increases on the right ventricle are often greater than comparable pressure workload increases in the left ventricle, associated with hypertension in the systemic circuit.

For this reason, the right cardiac ventricle is vulnerable to failure when it is subjected to high pressure loads in a variety of occupational pulmonary disorders.

LIST OF AGENTS THAT CAUSE OCCUPATIONALLY RELATED COR PULMONALE

Acute cor pulmonale may be associated with any disorder causing severe alveolar hypoxia including pulmonary edema associated with toxic exposures.

Documented Causes of Chronic Cor Pulmonale

1. Free silica (silicon dioxide) including quartz, flint, granite, sandstone, slate, and diatomaceous earth
2. Silicates: talc, kaolin
3. Asbestos
4. Beryllium
5. Coal mine dust
6. Tungsten carbide
7. Antigenic agents that cause allergic alveolitis

Probable Causes of Chronic Cor Pulmonale

1. Cadmium
2. Graphite
3. Hemp
4. Uranium mine dust

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

(See chapters on these entities)

1. Free silica
2. Silicates
3. Asbestos
4. Beryllium
5. Coal mine dust
6. Tungsten carbide
7. Allergic alveolitis
8. Cadmium
9. Graphite
10. Hemp, cotton, and flax workers
11. Uranium mine dust
12. Nitrogen oxides

EPIDEMIOLOGY

The epidemiology of cor pulmonale in occupational pulmonary disorders is largely the consequence of the epidemiology of individual disorders.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF COR PULMONALE

No credible data for cor pulmonale are available for any occupational pulmonary disorder because the diagnosis is often made only at autopsy and postmortem examinations are not performed on most workers. Cor pulmonale is difficult to detect in its early stages by commonly available, noninvasive clinical and laboratory techniques. Clinical surveys of at-risk populations have almost never used diagnostic techniques that would detect any but the most advanced cases of cor pulmonale. The little information that is available is summarized in Table X-1.

PATHOLOGY

The pathology and genesis of occupationally induced pulmonary vascular disease can only be understood against the background of normal changes in vascular structure with age. No significant resistance resides in the large, elastic pulmonary arteries, but atherosclerosis (in them) sometimes reflects an increased resistance in the more peripheral, smaller pulmonary arteries. The structure of muscular pulmonary arteries has great influence on pulmonary vascular resistance. In normal adults, the thickness of the muscular artery walls is similar in the upper and lower lobes of the lungs and uniform from beginning to end in individual muscular arteries (55). By contrast, such thickness varies greatly from one muscular arterial segment to another in aged nonsmokers and in middle-aged cigarette smokers (55). These segmental changes are mainly due to the uneven deposition of collagen and longitudinally oriented smooth muscle in the walls of the arteries. Between the ages of 30 and 70, the collagen content of pulmonary muscular artery walls increases in nonsmokers from 8% of total wall constituents to 25%. The comparable change in cigarette smokers is from 15% to 40% (38).

Longitudinally oriented smooth muscle increases with age in the walls of muscular pulmonary arteries. It appears sooner and is more extensive in cigarette smokers than in nonsmokers (38). In themselves, the collagen and longitudinally oriented muscles appear to have little functional significance. For example, there is no significant increase in the frequency of cor pulmonale if these vascular lesions are the only vascular ab-

Table X-1
POPULATIONS AT RISK OF DEVELOPING COR PULMONALE

Agent or Disorder	Population at Risk	Prevalence of Cor Pulmonale
1. Free silica	Those exposed to free silica and diatomaceous earth (11)(56).	No prevalence studies published, but cor pulmonale usually present when pulmonary fibrosis is both severe and widespread.
2. Silicates	The chemical composition of talc and exposures to it vary so greatly it is not possible to precisely define the populations at risk.	Kleinfeld et al. reported that 27% of one group of talc workers followed for 29 years died of pneumoconiosis and its complications, mainly cor pulmonale (23). The frequency of pulmonary parenchymal disease and cor pulmonale was apparently even higher in earlier years (24). In most industrial settings where talc is used, cor pulmonale is probably rare (21). Workers with kaolin pulmonary fibrosis can have cor pulmonale (61).
3. Asbestos	All population groups that have sustained contact with asbestos.	No prevalence data have been published for cor pulmonale, but some workers with advanced pulmonary parenchymal disease have cor pulmonale (1).
4. Beryllium	The U.S. Beryllium case registry should provide such data but it does not. Most current cor pulmonale is the result of sustained contact with beryllium as an antigen.	No prevalence data have been published, but some individuals with advanced pulmonary parenchymal disease develop cor pulmonale (15). Hansan et al. have reported that 16% of individuals with chronic beryllium pulmonary disease develop heart failure, but they gave no indication what proportion of these cardiac failures were related to cor pulmonale (19).
5. Coal mine dust	At least 6 different pulmonary disorders in coal workers can contribute to cor pulmonale. In general, coal workers exposed to substantial free silica and those who develop chronic bronchitis and/or emphysema are at risk of cor pulmonale.	In a study of 178 Appalachian bituminous miners who died between 1960-1968, 58% had moderate or severe cor pulmonale (40). In a much larger unpublished study of cases collected prospectively since 1970, less than 5% of miners of low rank Appalachian bituminous coal had cor pulmonale (37). Cor pulmonale has a higher prevalence among higher rank bituminous and anthracite coal miners, but exact figures are not available (26).
6. Tungsten carbide	Several studies have reported diffuse, interstitial, pulmonary fibrosis in some workers (8)(14).	No prevalence data are available.

Table X-1 (Continued)
POPULATIONS AT RISK OF DEVELOPING COR PULMONALE

Agent or Disorder	Population at Risk	Prevalence of Cor Pulmonale
7. Allergic alveolitis	All farm and mushroom workers exposed to the fungal antigens. All cork workers exposed to these antigens.	No prevalence data for cor pulmonale are available because most of the cases are sporadic in their appearance.
8. Cadmium	Acute cor pulmonale follows acute pulmonary edema resulting from large exposure to cadmium fumes.	Interstitial pulmonary fibrosis develops in a few individuals who are exposed to such fumes but no data have been published on the prevalence of chronic cor pulmonale.
9. Graphite	There is one published case of cor pulmonale in an individual who had severe granulomatous lung disease due to graphite exposure (28).	There are non-U.S. reports of up to 23% of graphite workers having dyspnea and cough, but no data on the prevalence of cor pulmonale (28).
10. Byssinosis	Individual cases of cor pulmonale have been reported in hemp workers (4).	It is not known if there is any increase in cor pulmonale in cotton workers. There may be an increase in hemp workers, but no prevalence data have been published (4).
11. Uranium mine dust	Most underground uranium miners.	Trapp et al. reported in 1970 that 4 out of 27 uranium miners had pulmonary arterial hypertension during exercise (57). No other prevalence data are available.
12. Nitrogen oxides	All workers who have large exposures.	A large exposure to nitrogen dioxide can produce acute pulmonary edema which in turn produces acute cor pulmonale (50).

normalities in the lungs (38). It is important that these pulmonary arterial changes, due to age and smoking, not be attributed to occupational exposures.

Pathophysiologic Causes of Pulmonary Hypertension Which May Be Associated With Occupational Exposures

Emboli—There are a large number of substances that can embolize to the pulmonary arteries and capillaries. Only a few are related to occupational exposures. The most frequent are bone marrow and fat that result from bone and adipose tissue trauma at the workplace (6). Gas emboli occur in divers. When repeated, such gas emboli produce occlusive sclerotic lesions in the pulmonary arteries of experimental animals. It is not known if similar lesions develop in humans.

Hypoxia—Alveolar hypoxia is probably the commonest cause of chronic pulmonary arterial hypertension in the United States. A list of occupationally related disorders to which alveolar hypoxia contributes would include fumes and gases that induce acute pulmonary edema; occupations that require residence at high altitude; brain stem trauma that affects central mechanisms of respiratory control; and by far the most common, disorders that obstruct the airways and lead to uneven distribution of inspired air. All of these disorders decrease alveolar levels of oxygen. Adjacent pulmonary arteries have a characteristic response. They constrict and in time develop a coat of hyperplastic and hypertrophied smooth muscle fibers (20)(39)(40). Pulmonary vascular resistance increases. Muscular hypertrophy and hyperplasia are reversible if normal alveolar oxygen levels are restored (9)(45). Most occupational diseases responsible for severe alveolar hypoxia cannot be completely reversed (39), and any improvement in the pulmonary arterial lesions may require the use of supplemental oxygen.

Both genetic and acquired factors appear to influence the pulmonary vascular response to alveolar hypoxia. Some individuals living at high altitude have pulmonary arterial pressures as low as those found at sea level while others have very high pressures (35)(36)(60). Such genetically based differences in the pressor response to alveolar hypoxia also appear to influence the outcome of patients with airways obstruction and pulmonary emphysema. In individuals with

severe emphysema, cardiac failure due to cor pulmonale develops later and survival is longer in those who have only a small pulmonary arterial pressor response to alveolar hypoxia than in those who have a larger pressor response (27).^{*} The intimate mechanism involved in the pulmonary arterial pressor response to alveolar hypoxia is not fully known, but it appears to be locally mediated through the adventitia of the arteries. Prostaglandin release may be involved (58). It is important to note that thrombotic or occlusive sclerotic lesions are rare in the pulmonary arteries of individuals with hypertension due to alveolar hypoxia. The vasoconstrictor effects of alveolar hypoxia are potentiated by acidosis.

Finally, the wall of the pulmonary artery can be made hypoxic with resultant chronic constriction and muscular hypertrophy in a number of occupational disorders in which environmental materials (e.g., dust macules) collect around the artery (40). The functional significance of this mechanism has not been assessed in most occupational pulmonary disorders because quantitative studies have not been undertaken.

Obliterative Lesions—Many different lung diseases include inflammatory or fibrotic processes that engulf and then destroy blood vessels. Such lesions probably make a major contribution to cor pulmonale in some diseases, but this has not been proven by quantitative, morphologic studies.

It is not enough to describe types of pulmonary vascular lesions associated with occupational disorders. Such listings give no clues to the relative functional importance of various lesions. There are additional problems. The arterial medial hypertrophy induced by hypoxia is a major factor in the development of cor pulmonale in many occupational lung disorders. Because increased pulmonary blood volumes commonly dilate hypertrophied arteries, the arterial wall does not appear unusually thick and the hypertrophy is usually not recognized.

There are further difficulties in interpreting the significance of pulmonary vascular abnormalities in occupational lung diseases. Both surgeons and pathologists are apt to select lung tissues that have obvious gross abnormalities for

^{*}Individuals with advanced cirrhosis of the liver have little or no pressor response to alveolar hypoxia (10). The mechanism of this loss is unknown. Cirrhosis of the liver can be occupationally induced, e.g., those who use carbon tetrachloride.

microscopic analysis. Obliterative vascular lesions are apt to be both more extensive and severe in such samples than in the lungs as a whole. Finally, emboli are often unevenly distributed to the pulmonary vascular bed so that many microscopic sections must be taken from different areas of the lungs to assess their number and role in changing pulmonary vascular resistance. With the partial exception of coal workers' pneumoconiosis, published analyses of occupational lung diseases are inadequate for quantitative distinctions. For many occupational lung diseases there is no published information at all.

With so little information published on occupationally induced cor pulmonale, another approach must be used to assess its possible impact on the work force. This can be done by identifying major disease processes in various occupational lung disorders, and then predicting probable extant pulmonary vascular lesions.

Before describing (published) pulmonary vascular abnormalities in individual occupational disorders, it is useful to describe vascular abnormalities associated with major diseases that are constituents of most occupational lung diseases. The most frequent occupationally induced pulmonary disorder in the United States is bronchitis/bronchiolitis. It is found with exposures to a wide range of environmental agents. Its anatomic correlates are mucous gland hyperplasia, goblet cell metaplasia, increased mucous production, inflammation and sometimes a mild fibrosis in the airways. In autopsy studies, these findings correlate poorly with functionally significant chronic airways obstruction present during life (32)(51). Cor pulmonale almost never develops with chronic bronchitis/bronchiolitis in the absence of airways obstruction (52)(53). The presence of emphysema correlates more closely with airways obstruction. Emphysema without airways obstruction reportedly does not cause cor pulmonale (54). Functionally significant airways obstruction must usually be present if cor pulmonale is to develop in patients with bronchitis/bronchiolitis and/or emphysema (25)(31)(32)(52)(54).

Alveolar hypoventilation and ventilation/perfusion imbalances which cause hypoxemia are not easily correlated with the morphologic abnormalities. Thus, although the level of pulmonary artery pressure is correlated with the severity of arterial hypoxemia in patients with chronic

airways obstruction (7), the relationship between right ventricular weight and anatomic emphysema is weak (31). The pulmonary vascular abnormality mainly responsible for cor pulmonale in cases of airway obstruction is medial hypertrophy in small muscular arteries (39). Such hypertrophy is potentially reversible because several weeks of oxygen administration sometimes lowers pulmonary arterial pressures in patients with severe airways obstruction (7).

Alveolar hypoventilation, hypoxia, and consequent pulmonary arterial hypertension are probably responsible for the acute cor pulmonale occasionally reported in cases of occupationally induced acute pulmonary edema. Acute cor pulmonale is probably far more common in cases of acute pulmonary edema than has been reported (50).

Destruction of blood vessels is another major mechanism involved in the genesis of pulmonary arterial hypertension in occupational lung disease. Such disorders are usually inconsistently distributed throughout the lobes of the lungs which makes quantitation of the vascular destruction difficult. The functional significance of such vascular destruction is also difficult to assess, because as much as two-thirds of the total pulmonary vascular bed must be destroyed to produce pulmonary arterial hypertension (62). Thus, the striking obliterative vascular lesions present in many occupational pulmonary disorders may (sometimes) have less functional significance than authors have claimed.

Pathology of Specific Disorders

Silicosis

In silicosis, macrophages characteristically phagocytize toxic particles, move to new sites, die, release the toxic particles and the cycle is repeated. Each cycle produces fibrosis which spreads, often concentrically. The macrophages characteristically invade the adventitia of pulmonary vessels which contributes to the vascular obliteration characteristic of the disorder (44)(56) (Figure X-1). Both the direct toxicity of the silicic acid released by the silica particles and immunologic mechanisms may be involved in the genesis of the fibrosis. Pulmonary vessels often display an intimal fibrosis and published reports have frequently mentioned thrombi in pulmonary arteries (48) (Figure X-2). It would be unwise to accept these obliterative and thrombotic



Figure X-1. Macrophages with silica particles and chronic inflammatory cells have infiltrated the wall and obliterated a segment of a muscular pulmonary artery in a case of acute silicosis (aldehyde fuchsin elastic stain, X560).



Figure X-2. Marked intimal fibrosis in a muscular pulmonary artery. The artery is entering a large fibrotic area in a case of chronic pulmonary silicosis (aldehyde fuchsin stain, X225).



Figure X-3. A small pulmonary artery enters a granulomatous area and is obliterated in a case of asbestosis (aldehyde fuchsin, X225).

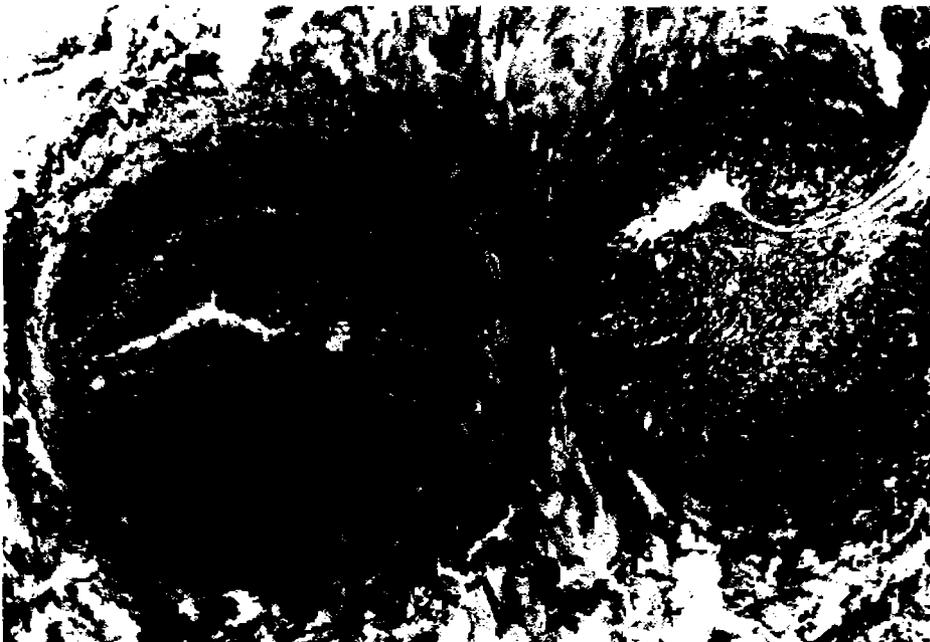


Figure X-4. Marked intimal fibrosis is visible in this muscular pulmonary artery. The artery is entering an area of dense fibrosis in a case of asbestosis (aldehyde fuchsin, X360).



Figure X-5. A small muscular pulmonary artery is invested by a mantle of coal dust in coal workers' pneumoconiosis (trichrome, X200).

lesions as the sole cause of pulmonary arterial hypertension and cor pulmonale in silicosis. Airways obstruction as well as pericardial and other forms of emphysema are common in the disorder, so alveolar hypoxia may make a contribution to the cor pulmonale (11)(44)(48)(56).

Silicates

Talc is not a uniform commercial product. Some commercial talc is mixed with other silicates such as serpentine, tremolite and anthrophyllite as well as other ingredients such as carbonates. The extent to which each of these contributes to the granulomatous process characteristic of talcosis is not precisely known. In addition, the length of some fibers in talc mixes (such as tremolite) reportedly affects the fibrogenic properties of the product (23). Commercial talc may also contain traces of quartz. Usually the amount of reticulum and collagen in talc granulomas is somewhat less than that found in strictly silicotic lesions. The extensive arterial obliteration found in silicosis is not so often encountered in talcosis (56). However, endarteritis with vascular obliteration is common at the edge

of granulomas and many cases of chronic cor pulmonale have been reported in workers exposed to talc (23)(24). Other studies have reported no cor pulmonale in talc workers despite long exposures to the agent (21).

Asbestos

Asbestos belongs to a group of silicate minerals known as amphiboles. The production and use of asbestos has increased greatly throughout the world in the last two decades. When inhaled, the needle-like fibers mainly pass to the lower lobes where the greatest damage occurs. In severe cases the lower lobes are largely replaced by a mass of grey fibrous tissue. The granulomas may start in bronchioles, alveolar ducts, or alveoli. A diffuse, interstitial, alveolar fibrosis develops in some cases when the asbestos particles are very small (Figures X-3 and X-4). Severe airways obstruction and emphysema are not usually a prominent feature in asbestosis, so alveolar hypoxia and cor pulmonale are not as common as in silicosis. Clinically, signs of right sided cardiac failure are usually a very late feature of the disease (1)(12). More specific information about



Figure X-6. Progressive massive fibrosis (PMF) in a 40-year-old coal miner. Blood vessels are usually completely obliterated in such lesions. (Gough section).

vascular lesions and cor pulmonale is absent from the literature.

Beryllium

Chronic beryllium disease of the lungs is characterized by a chronic interstitial pneumonitis, often accompanied by focal granulomatous lesions which resemble sarcoid (15). The chronic disease has an immunologic origin. There is no doubt that a portion of the victims develop cor pulmonale, but published accounts have little to say about pulmonary vessels (15)(19). Seventeen of 124 patients with chronic beryllium disease in one series had pulmonary emboli or infarcts at autopsy (15). This is not a large number considering many of these individuals had protracted cardiac failure prior to death (15). It has been reported that some pulmonary arteries are obliterated by the granulomas in the disorder, but their relative number

is unknown. Published information is not adequate to estimate the frequency of cor pulmonale or to speculate on its exact causes when present.

Coal Workers' Pneumoconiosis

Far more is known about the frequency and causes of cor pulmonale in coal workers' pneumoconiosis than about cor pulmonale in any other occupational lung disease. Several types of pulmonary vascular abnormalities are found in the lungs of coal workers with pneumoconiosis: A) lesions related to the primary dust macule; B) lesions related to fibrotic nodules and progressive massive fibrosis (PMF); C) lesions related to other pulmonary disease processes. Only one of these lesions (A) is relatively specific for coal workers, and its functional significance may be small. Coal dust macules evolve by the incorporation of dust-filled macrophages into the walls of respiratory bronchioles and adjacent alveoli. In this process the associated small muscular artery is invested by the mantle or cuff of coal dust (Figure X-5). It has been postulated that such mantles lead to a perfusion derangement. Quantitative analysis has shown that arterial medial muscle mass increases significantly in those artery segments inside the dust macules (40). The increase is mainly due to hypertrophy of individual arterial medial muscle fibers. In young miners, this muscular hypertrophy is not associated with cor pulmonale, an indication that by itself, the hypertrophy does not have great functional significance.

Obliterative vascular lesions are often associated with fibrotic nodules and progressive massive fibrosis in coal workers' pneumoconiosis. Occluded and destroyed blood vessels are common in completely collagenized nodules and in areas of progressive massive fibrosis (Figures X-6, X-7). These vascular lesions are most frequent in anthracite workers (17)(18).

Most of the cor pulmonale in coal workers appears related to airways disease and emphysema (40). The emphysema is of several types: focal, centrilobular, pericatricial, and mixed. The predominant vascular lesion in miners who develop cor pulmonale is an increase of circularly-oriented muscle in the media of muscular pulmonary arteries (40). This is presumably due to alveolar hypoxia (39). Although studies show overall correlations between degrees of emphysema and chronic cor pulmonale, such correlations are often poor in individual patients. This may be due to genetic differences between in-



Figure X-7. Collagen has replaced most other constituents in a coal dust macule. Blood vessels are obliterated in such lesions (trichrome, X130).

dividual miners which appear to significantly influence the pulmonary vascular pressor response to alveolar hypoxia (35). Individual variations in this pressor response seem to influence the clinical course of emphysema. In individuals with severe emphysema, cardiac failure develops later and survival is longer in those who have only a small pulmonary arterial pressor response to alveolar hypoxia (27).

Tungsten Carbide

Two forms of disease are produced by exposure to cobalt which is a contaminant in tungsten carbide. One resembles berylliosis in that it has both an interstitial and a granulomatous component. The other is a disorder that produces airways constriction. A few cases of cor pulmonale have been reported in individuals with the diffuse, interstitial form of the disorder in which many capillaries and small arteries are presumably replaced by fibrous tissue (8)(14). Published information is so sketchy that the exact nature of the pulmonary vascular lesions responsible for the cor pulmonale is not known.

Allergic Alveolitis

This describes a series of disorders produced by the inhalation of antigenic materials which

produces an inflammatory process in the alveolar wall. The lesions are often complex which may explain why the vascular lesions responsible for occasional cases of cor pulmonale have not been described. Inflammation often involves the bronchioles as well as the alveoli, and sometimes appears in the form of noncaseating granulomas that resemble sarcoid. In rare instances, lesions progress to severe interstitial fibrosis and even honeycomb lung. Patients tend to hyperventilate during the acute phase of the disease and may have a slight increase in pulmonary vascular resistance and pulmonary arterial pressure. Severe pulmonary arterial hypertension and cor pulmonale develop only in advanced cases with severe interstitial fibrosis. It is likely that combinations of airways obstruction and vascular obliteration are responsible for the right ventricular hypertrophy and failure.

Cadmium

An acute exposure to high concentrations of cadmium fumes results in acute pulmonary edema and acute cor pulmonale (16). Workers chronically exposed to cadmium fumes may develop a mild interstitial fibrosis and perhaps emphysema, without much obstructive airways dis-

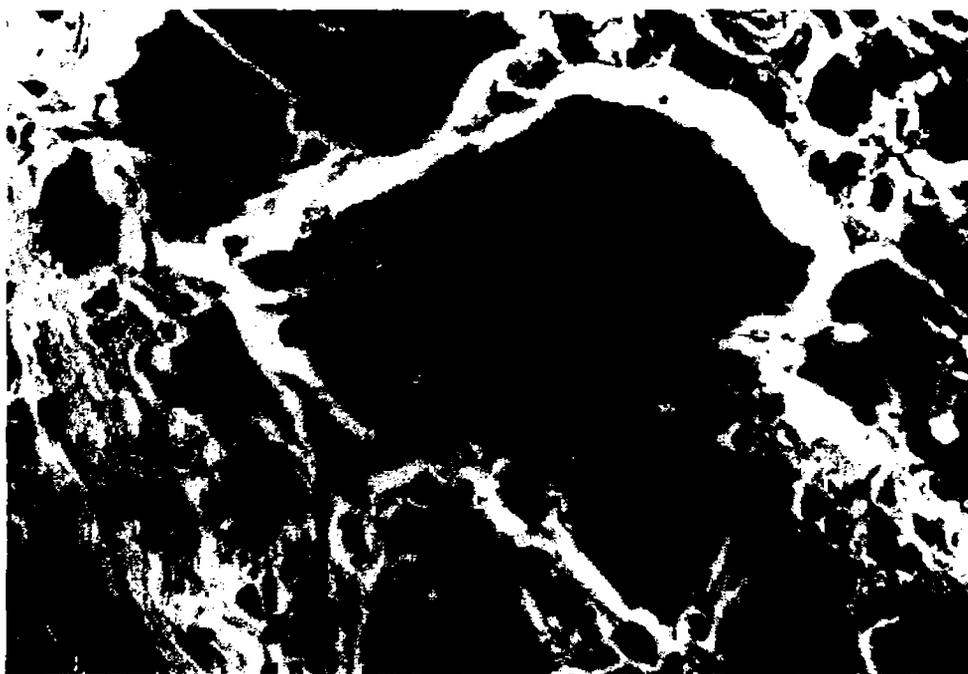


Figure X-8. This lung section from a graphite worker shows giant cells with enclosed graphite crystals (H&E, X1075).

ease. Cor pulmonale has not been reported in these latter cases.

Graphite

Synthetic or naturally occurring graphite can cause remarkable granulomatous lesions in the lungs, often perivascular in location (22)(28). A few workers have developed cor pulmonale (28). Not enough information has been published to identify the nature of the vascular lesions responsible for the cor pulmonale (Figure X-8).

Byssinosis

Cotton, flax, and hemp workers sometimes develop byssinosis. Many workers are involved and large epidemiologic studies have been published (29)(30)(59). The disease is usually characterized by a reversible airways obstruction accompanied by signs and symptoms of bronchitis. An increased mortality has been reported in workers heavily exposed to such dusts for long periods (49). A few reportedly develop chronic airways obstruction and some hemp workers have reportedly died with cor pulmonale (4). Nothing has been reported on the nature of the pulmonary vascular abnormalities in these fatal cases.

Nitrogen Oxides

Nitrogen dioxide can produce acute pulmonary edema with consequent acute cor pulmonale.

CLINICAL DESCRIPTION OF COR PULMONALE

“Of the many disease entities that affect the heart, the internist and even the cardiologist is least familiar with the entity of cor pulmonale. . . there is a definite lack of prevalence data because of the lack of uniform diagnostic criteria and reporting” (13).

Symptoms

Acute cor pulmonale is usually produced by embolism or acute pulmonary edema. A number of occupational exposures produce such edema. The symptoms referable to cor pulmonale are obscured in such cases by the dyspnea and discomfort associated with the edema.

Chronic cor pulmonale—An early diagnosis is made only when it is recognized that a pulmonary disorder in a patient can culminate in pulmonary hypertension. Overt right sided cardiac failure is often a late feature of chronic cor pulmonale. When it develops, such failure is

often insidious in onset unless it appears during the course of an acute respiratory tract infection. Frequently, diagnosis is made only when shortness of breath fails to resolve after an acute infection is controlled. Patients with marked pulmonary ventilation/perfusion imbalances and gas diffusion defects may also experience somnolence due to hypercapnia.

Signs

The signs of right ventricular hypertrophy are a cardiac thrust along the left sternal border or just below the sternum and a fourth heart sound, arising in the hypertrophied right ventricle at the same site. Pulmonary hypertension is often accompanied by a loud second heart sound in the second left interspace adjacent to the sternum and a cardiac thrust in the same area. Sometimes the pulmonic valvular ring dilates and the murmur of pulmonic valvular insufficiency can be heard. If the right ventricle fails, a right ventricular gallop and tricuspid valvular insufficiency murmur may appear. Hydrothorax is rare but dependent edema is commonly present. Systemic venous congestion is often evident.

Natural History Including a Consideration of Reversibility and Progression

Since overt signs and symptoms of cor pulmonale frequently appear during the course of an acute respiratory infection, improvement often follows successful treatment of the infection. More fundamental questions relate to the causes of increased pulmonary vascular resistance and its reversibility. Pulmonary hypertension whose main cause is alveolar hypoxia, is potentially reversible, because structural changes in the pulmonary arteries involve only a hypertrophy of medial smooth muscle. This potential reversibility is confirmed by the finding that some individuals with hypoxia-induced pulmonary arterial hypertension have a decrease in pulmonary vascular resistance following the sustained administration of oxygen (7). In general, cardiotonic drugs are not effective in relieving right-sided cardiac failure unless oxygenation is improved. If adequate arterial blood oxygen tension is restored, it is often possible to discontinue diuretics and digitalis.

Since airways obstruction is the most common cause of low alveolar and arterial blood oxygen tension, the course of pulmonary hypertension and the resultant cor pulmonale depends on the reversibility of the obstruction. The funda-

mental causes of the obstruction are at least partially irreversible, i.e., destruction of airways and loss of the radial traction that keeps them open. Respiratory tract infections add to the obstruction by narrowing or plugging the airways with mucus and inflammatory debris. Treating the infections often partially alleviates the obstruction. Usual treatment measures are hydration, antibiotics, and bronchodilators. When respiratory failure supervenes, mechanical aids to respiration are often needed.

Treatment for cardiac failure is usually instituted when there is evidence of right-sided failure. Methods include digitalis, diuretics, low salt diet, and phlebotomies to bring hematocrits and blood volumes to more normal levels. Diuretics have to be carefully administered because potent diuretics (like ethacrynic acid) may cause metabolic alkalosis which depresses the CO₂ stimulus to the respiratory center. The most important therapeutic measure in a patient with severe hypoxemia is the administration of supplemental oxygen.

Complications of cor pulmonale are difficult to treat when the increase in pulmonary vascular resistance is mainly due to blood vessel destruction. This applies particularly to cases of silicosis in which silica-bearing macrophages have invaded the adventitia of arteries and led to widespread fibrous obliteration of vessels.

Appropriate Laboratory Investigations

The diagnosis of cor pulmonale can be made with certainty by right-sided cardiac catheterization. Typically such catheterization shows pulmonary arterial hypertension, a normal pulmonary arterial wedge pressure, and an increased right ventricular diastolic filling pressure—when ventricular failure is present. Roentgenographic analyses have value in diagnosing cor pulmonale, but they are often not definitive. A perfused peripheral pulmonary arterial tree is perhaps the most definitive diagnostic finding when the pulmonary arteries are obstructed. Enlarged central pulmonary arteries coupled with a known pulmonary disorder raise the suspicion of pulmonary arterial hypertension. Selective right-sided cardiac enlargement is difficult to recognize on roentgenographic examinations, but should be suspected in cases where heart size increases during bouts of acute respiratory insufficiency.

The electrocardiogram is sometimes helpful in making a diagnosis of cor pulmonale, mainly when it is advanced. It is not as useful in many

occupational disorders as in those of nonoccupational origin. A high proportion of individuals with cor pulmonale due to occupational lung disease have chronic airways obstruction. Reportedly, the diagnosis of cor pulmonale can be made by ECG on only about one quarter of the patients who have the disorder secondary to obstructive airways disease (13). This is apparently due to hyperinflated lungs and to the episodic nature of the pulmonary hypertension in many patients with airways obstruction. The ECG is somewhat more useful in diagnosing cor pulmonale due predominantly to obliterative pulmonary vascular disease. ECG patterns that suggest chronic cor pulmonale include P-pulmonale in leads II, III, IV; AVF, right axis deviation; R:S ratio in $V_1 > 1$, in V_5, I , and in right chest leads; and partial or complete right bundle branch block (13)(54). These criteria are moderately specific but insensitive. Recently introduced radionuclide technology can also be used to demonstrate cor pulmonale. Patients with cor pulmonale reportedly have a reduced right ventricular ejection fraction (3).

The echocardiograph can detect some cases of cor pulmonale. Both hypertrophy and dilatation can sometimes be detected in the right ventricle by this means. Such patients often have abnormal motion in the pulmonic valve, i.e., an absent or decreased alpha dip and a rapid systolic opening velocity of the valve. Most echocardiographers have difficulty making the diagnosis of chronic cor pulmonale unless right ventricular hypertrophy is moderate or severe. Thus, the technique is not suitable for screening programs designed to detect early thickening of the right ventricular wall.

DIAGNOSTIC CRITERIA

The post mortem diagnosis of acute cor pulmonale rests on finding a dilated right ventricle. Flattening of the trabeculae carneae usually makes this diagnosis easy. Chronic cor pulmonale is recognized by finding myocardial hypertrophy in the right ventricle wall. This latter diagnosis is not easy to make when the hypertrophy is mild or when the ventricular wall is dilated. Comparisons with the left ventricular wall are not always helpful because left ventricular hypertrophy and failure are common in cor pulmonale (31). A more certain diagnosis can be made by separately dissecting and weighing the two cardiac ventricles and then comparing

them with body weight (31)(43). Such dissections are rarely undertaken and are one reason there is so little prevalence data on cor pulmonale for occupational pulmonary disorders. Finally, many pathologists do not recognize mild or even moderate degrees of right ventricular hypertrophy because they do not consider a diagnosis of cor pulmonale. Or when they do recognize the abnormality, they do not connect it with the occupationally related pulmonary parenchymal disorder. This accounts for the many reports in the literature of advanced occupational lung disease without any recognition of abnormalities in the right heart.

Even greater problems are posed by the inadequate methods available for making the diagnosis of cor pulmonale in living patients. Cardiac catheterization is the most definitive method for detecting cor pulmonale, but it is expensive and involves risks to the patient. It is therefore unsuitable for mass screening and prevalence studies. Echocardiography is noninvasive but as used by most cardiologists detects only advanced right ventricular hypertrophy. Its use in surveys would greatly underestimate the prevalence of chronic cor pulmonale. Physical examination evidences of chronic cor pulmonale are usually late manifestations of the disorder and are usually absent when patients die of nonpulmonary disorders. Chest radiographs are unreliable in recognizing most mild and many moderate cases of chronic cor pulmonale. The diagnosis can reliably be based on the ECG only when obstructive airways disease is absent and the cor pulmonale advanced. The true prevalence of cor pulmonale will not be known for any occupational disease until inexpensive, sensitive, practicable, and noninvasive techniques are developed to make the diagnosis in life.

METHODS OF PREVENTION

Methods for preventing acute cor pulmonale depend entirely on avoiding contact with toxic fumes and gases that produce acute pulmonary edema and on avoiding the trauma that results in fat and bone marrow emboli. Because obstructive airways disease is the most common cause of chronic cor pulmonale in most occupational lung disease, methods for preventing chronic cor pulmonale are largely those required to prevent individual occupational pulmonary disorders. A public health program that delays the appearance and reduces the frequency of chronic air-

ways obstruction—through enforcement of air pollution standards; anti-smoking education; a monitored system of pulmonary function testing; etc.—should reduce the prevalence of chronic cor pulmonale in occupational lung disease.

RESEARCH NEEDS

1. The most obvious need is for prevalence data. This will be both expensive and difficult to obtain. To obtain postmortem data, a program of sponsored autopsies like that operated by ALOSH for coal workers is needed. Hearts would probably have to be collected and examined at one central location to insure uniform dissections and weighing. Obtaining clinical prevalence data on cor pulmonale presents formidable problems. The only definitive available method for making the diagnosis is cardiac catheterization, and it is unsuitable for epidemiologic studies because of its expense and risk to patients. Studies should be undertaken to determine if ECG, in combination with echocardiography and x-ray, would be suitable epidemiologic tools. The recently introduced radionuclide techniques are another possible diagnostic tool.
2. The most common mechanism responsible for cor pulmonale in occupational lung disease is alveolar hypoxia. Possible biochemical mediators and mechanisms of hypoxia-induced pulmonary hypertension, such as prostaglandins, histamine receptors, calcium transport, etc., need further investigation.
3. New drugs are needed to dilate pulmonary arteries. All currently effective drugs have side effects that are too serious to permit long-term use. Some dilate systemic as well as pulmonary arteries. All have the inherent limitation that they permit perfusion of poorly ventilated areas of the lung and thereby cause hypoxemia. Despite these limitations, there are substantial numbers of patients whose high levels of pulmonary vascular resistance are a prime threat to their survival. More effective, safe pharmacologic vasodilator agents would likely benefit many of these individuals.
4. There are almost no data in the literature quantitating the individual pulmonary vascular lesions responsible for cor pulmonale in occupational lung diseases. Coal workers' pneumoconiosis is a partial exception; CWP data confirmed that alveolar hypoxia, rather than fibrotic and obliterative lesions, was primary responsible for cor pulmonale. Similar studies are needed for other occupational lung diseases.
5. In the first section of this report there is an outline of pulmonary vascular changes related to aging and cigarette smoking. These changes in themselves do not significantly increase pulmonary vascular resistance and cause cor pulmonale. They might, however, potentiate vascular damage due to occupational agents and thereby accelerate the development of cor pulmonale. Postmortem material for this line of research is readily available and should be studied.
6. No systematic studies have been published detailing specific effects—on human pulmonary arteries and veins—of common air pollutants in our industrial environments. Not only should such studies be undertaken, but possible interactions between these air pollutants and occupational agents need to be examined.
7. The list of documented occupational lung disorders involving cor pulmonale is short. The actual incidence of occupational disorders involving cor pulmonale is undoubtedly substantial. Systematic studies should be undertaken to search for these associations. Most such (currently unrecognized) associations are likely to be found in occupational disorders in which airways obstruction is a major feature.
8. Quantitative studies have shown that the microcirculation of the left ventricle is affected by cigarette smoking. Smoking accelerates the replacement of normal, circularly oriented, smooth muscle in small artery walls by collagen and longitudinally oriented muscle (42). There is strong evidence that these small artery lesions impair ventricular contractility when a severe pressure load is imposed on the ventricle (41). Such studies should be repeated on the right ventricle to determine if lesions in the small intramy-

cardial arteries contribute to the development of right-sided cardiac failure in patients with chronic pulmonary arterial hypertension.

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APPENDIX

THE U.S. POPULATION AT RISK TO OCCUPATIONAL RESPIRATORY DISEASES



APPENDIX

The U.S. Population-At-Risk to Occupational Respiratory Diseases

Wayne T. Sanderson

In the assessment of agents associated with occupational diseases, the *population-at-risk* indicates the enormity of the problem in the workplace that future research and health needs must address.

This table juxtaposes hazardous agents with diseases they cause or provoke; conjoins these agents with involved occupations; and estimates the number of workers in these occupations potentially at risk to exposure from the associated agents. This approach provides a quick reference to the causes of each disease; the occupations where a prevalence of disease might be expected; and a ranking based on the number of people exposed. The reader should bear in mind that the agents listed may not constitute all factors contributing to the diseases (other etiologic factors may be equally weighty), nor will all workers involved in the listed occupations be exposed to the associated agents. Additionally, only the major industries and occupations in which the agents are used are included in this table; therefore, a particular disease may be exhibited in a job not delineated.

The *population-at-risk* estimate should be taken as an approximation of the number of workers who work closely with an agent and not the number of people who should be considered probable *cases* of disease. *Agents* listed are those which have been noted to contribute to or cause particular diseases. *Industries or Occupations*

associated with the agents listed are revised lists from the National Institute for Occupational Safety and Health (NIOSH) criteria documents, NIOSH publication No. 77-181, and epidemiological studies. *Estimates of population-at-risk* are from the NIOSH criteria documents, the National Occupational Hazard Survey (NOHS), and revised estimates based on census data and prevalence studies. Behind each number of estimated people exposed is a letter designation, indicating the source of that estimate:

- C** = estimates from NIOSH criteria documents addressed to the various agents.
- H** = estimates from the National Occupational Hazard Survey (NOHS) conducted by NIOSH in 1972-74.
- R** = estimates from census data and disease prevalence studies.

To simply state that an estimated number of people are occupationally exposed to a particular agent does not solve the complex problem of determining the true magnitude of the hazard. For this, an in-depth look at the concentrations, modes of exposure, and trends in use (among other things) should be considered. The value of these estimates is to indicate (1) where in the work force these toxic agents appear, and (2) the numbers of workers who *may* be exposed to hazardous agents.

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
Aluminosis	Aluminum (powdered metal)	aluminum alloy grinding aluminum smelting aluminum workers ammunition makers fireworks makers foundry workers petroleum refining plastic making rubber making	575,000 H
	[Exposure to aluminum and aluminum oxide is frequently associated with exposure to silica and dusts also]		
	Aluminum oxide	abrasive manufacturing catalyst makers metal grinders potteries refractories	500,000 H
Antimony Pneumoconiosis	Antimony Stibnite (antimony sulfide)	alloy manufacturing ceramic making drug manufacturing fireworks manufacturing leather mordanting mining and milling of antimony paint manufacturing pewter manufacturing pharmaceuticals rubber production textile manufacturing typesetting	1,350,000 H
Argyria	Silver and compounds silver cyanide silver fulminate silver nitrate	alloy manufacturing ceramics coin production chemical laboratory workers dental alloy makers drug manufacturing electrical equipment manufacturing food product equipment manufacturing glass making hair dye manufacturing hard solder makers ivory etching mirror making organic chemical manufacturing photographic workers water treatment	60,000 R
Asbestosis	Asbestos actinolite	brake and clutch lining manufacture and	1,500,000 R

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
	anthophyllite asbestos crocidolite tremolite	installation cement (asbestos) production and application demolition workers furnace and kiln lining insulation and fireproofing manufacture and installation mining and milling of asbestos paint production paper manufacturing plastic manufacturing plumbing power station workers roofing tile production and installation shipbuilding	
Asthma-like Illness "Pneumoconiosis"	Cobalt	alloy manufacturing catalyst workers ceramic manufacturing drug manufacturing electroplaters glass colorers nickel workers paint dryer manufacturing porcelain coloring rubber coloring synthetic ink manufacturing	250,000 H
Baritosis	Barium sulfate	animal oil refining baryta mining brick manufacturing ceramic manufacturing glass making ink manufacturing linoleum production lithopone making paint manufacturing plastic manufacturing soap making textile manufacturing tile manufacturing wax processors	800,000 H
Berylliosis	Beryllium and compounds ammonium beryllium fluoride beryllium carbide beryllium copper alloys beryllium fluoride	aerospace equipment manufacturing alloy manufacturing beneficiation of beryllium minerals beryllium ceramic products beryllium processing and	800,000 R

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
	beryllium hydroxide	refining	
	beryllium oxide	cathode ray tube	
	beryllium oxyfluoride	manufacturers	
	beryllium phosphors	chemical manufacturing	
	beryllium sulfate	electronic equipment	
	zinc beryllium silicate	manufacturing	
		gas mantle makers	
		metallurgical operations	
		missile technicians	
		nonferrous foundry	
		production	
		nuclear reactor workers	
		phosphor manufacturing	
		refractory material makers	
		tool and die manufacturing	
		welding and torch cutting	
		beryllium alloys	
Bird Breeders' Lung	Avian droppings	bird keepers	100,000 R
Bird Fanciers' Lung	Avian proteins		
Pigeon Breeders' Lung		pigeon breeders	
Byssinosis	Cotton dust	cotton classifiers	800,000 C
		cotton processing	
		carding	
		drawing & roving	
		ginning	
		growing & harvesting	
		opening, cleaning, picking	
		spinning, winding, twisting	
		spooling, beaming, slashing	
		weaving	
		cottonseed oil mill workers	
		cotton waste reclaimers	
		garnetting	
	Flax	flax carders	2,000 H
		flax mixers	
		flax workers	
		yarn makers	
	Jute	jute workers	3,000 H
	Hemp	hemp workers	1,000 H
	Sisal	carpet makers	2,000 H
		combers of sisal	

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		drawers of sisal rope makers sisal workers twine spinners	
Cer-pneumoconiosis	Ceria (cerium oxide)	alloy manufacturing ammonia production enamel manufacturing glass making graphic art workers ink manufacturing lighter flint makers metal refining mining and milling of cerium optical lens production phosphor production rocket fuel manufacturing textile manufacturing	7,000 H
Coal Workers' Pneumoconiosis due to Carbon	Carbon black	battery manufacturing carbon electrode makers carburization workers cement workers ceramics food processing ink manufacturing paint manufacturing paper production plastic manufacturing printing production, collection, and handling of carbon black rubber manufacturing	35,000 C
	Coal dust anthracite bituminous coal lignite seacoal	loading and transporting of coal mining and milling of coal	150,000 R
	Graphite	brake lining manufacturing cathode ray tube manufacturing commutator brush manufacturing crushing and milling of graphite crucible production electrode making explosive manufacturing foundries lubricant production	250,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		match production nuclear reactor workers paint manufacturing pencil lead making pigment manufacturing refractory material makers steel workers stove polish manufacturing	
	Lamp black	cement workers ceramic ware manufacture lamp black production and handling liquid-air explosive manufacture lubricating composition manufacturing steel making	UK
Coffee Workers' Lung	Coffee dust	coffee bean processors	12,900 R
Enzyme Workers' Lung	Bacillus subtilis (detergent enzymes)	detergent workers housewives laundry workers	175,000 + H
Epoxy Resin Workers' Lung	Phthalic anhydride	alizarin dye manufacture alkyd resin manufacture automobile finish makers cellulose acetate plastizers dacron fiber production epoxy resin workers erythrosin manufacture insecticide manufacture mylar plastic manufacture organic chemical synthesis phthalein manufacture plastics manufacture resin making vat dye makers vinyl plasticizer manufacture	54,000 R
Furriers' Lung	Hair dust (animal proteins)	furriers	4,700 R
Hard Metal Disease Tungsten Carbide Pneumoconiosis	Tungsten Carbon plus Cobalt	arc cutting hard metal manufacturing metal cutting milling of tungsten carbide with cobalt	60,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
	Metallurgical blending of tungsten and carbon with cobalt used as a binder		
Hypersensitivity Pneumonitis			
Farmers' Lung	Micropolyspora faeni (moldy compost) or hay	farmers, especially dairy farmers	2,800,000 R
Mushroom Workers' Lung	Thermoactinomyces vulgaris Thermoactinomyces viridis	clean out crews of mushroom bed houses	<1,000
Bagassosis	Thermoactinomyces saccharii (moldy sugar cane)	sugar cane workers	5,000 R
Maple Bark Strippers' Disease	Cryptostroma Corticale (moldy maple bark)	bark strippers loggers pulp mills sawmill workers	80,000 R
Malt Workers' Lung	Aspergillus claratus (moldy malt)	malt house workers	1,800 R 1,700 R
Suberosis	Penicillium frequentans (moldy cork dust)	cork workers	7,000 H
Cheese Washers' Lung	Penicillium caseii (cheese mold)	cheese workers	25,000 R
Woodworkers' Lung	Alternaria sp. (moldy wood chips)	carpenters construction workers joiners sawmill workers wood pulp workers	10,000 R
Sequoiosis	Pullalaria (moldy redwood dust)	loggers sawmills	<1,000 R
Paprika Splitters' Lung	Mucor sp. (paprika dust)	paprika splitters	
Wheat Weevil Disease	Sitophilus grainarius (wheat weevil) (infested wheat)		
Infectious Disease			
Anthrax	Bacillus anthracis	agricultural workers goat hide handlers renderies	>10,000 R

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		veterinarians wool handlers	
Brucellosis	Brucella sp.	agricultural workers consumers of unpasteurized milk or milk products meat packers slaughterhouse workers veterinarians	>10,000 R
Histoplasmosis	Histoplasma capsulatum	farm workers endemic in certain areas	
Tuberculosis	Mycobacterium tuberculosis	coal workers foundry workers hard rock miners medical laboratory workers nurses physicians saloon workers	UK (30,000 cases per year)
Metal Fume Fever	Antimony Cadmium Copper 1° agents Iron Magnesium Manganese Nickel Selenium Tin Zinc	brass founders copper and zinc melters welders zinc galvanizers zinc smelters	40,000 R
Neoplasms Nasopharyngeal Neoplasms	Chromium salts	alloy makers chemical laboratory workers electroplaters miners and millers pigment makers tanners	1,000,000 H
	Nickel	battery makers ceramic makers chemists dyers electroplaters enamellers ink makers magnet makers oil hydrogenators paint makers pen point makers spark plug makers stainless steel workers textile dryers	250,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		varnish makers welders	
	Nickel salts	nickel mining, smelting, refining	250,000 H
	Wood dust	carpenters furniture makers loggers plywood & structural wood producers sawmill workers woodworkers	775,000 H
No known pneumoconiosis demonstrated to be caused by fibrous glass alone.	Fibrous glass	aircraft workers construction workers glass workers glass fiber manufacturers insulation manufacturers laundry workers refrigeration workers shipyard workers	300,000 H
	Mineral wool	mineral wool manufacturers	3,000 H
No specific respiratory disease associated with the inhalation of Zirconium or its compounds	Zirconium or zirconium compounds	abrasive makers ceramic makers ceramic manufacturing crucible manufacturing deodorant manufacturing enamel manufacturing explosive manufacturing foundry workers glass makers incandescent lamp manufacturing metallurgists pigment manufacturing rayon spinneret makers refractory material makers textile waterproofers vacuum tube manufacturing	150,000 H
Occupational Asthma and Rhinitis		See chapter: Occupational Asthma & Rhinitis	
Polymer Fume Fever	Polytetrafluorethylene (teflon, fluon) (PTFE)	polytetrafluoroethylene producers and handlers cutters of metal welders	100,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
Porcelain Refinishers' Lung Isocyanate Disease	Hexa methylene diisocyanate	rubber workers ship burners textile processors wire coating workers	3,000 H
	Toluene diisocyanate (paint catalyst)	adhesive workers foam insulation workers isocyanate resin workers lacquer workers organic chemical synthesizers paint sprayers polyurethane manufacture	6,000 H
Pulmonary Neoplasms	Arsenic	alloy makers aniline color makers arsenic workers babbitt metal workers brass makers bronze makers ceramic enamel makers ceramic makers copper smelters drug makers dye makers enamellers fireworks makers gold refiners herbicide makers hide preservers insecticide makers lead shot makers painters paint makers petroleum refinery workers pigment makers printing ink workers rodenticide makers semiconductor compound makers silver refiners taxidermists tree sprayers type metal workers water weed controllers weed sprayers	150,000 C
	Bischloromethyl ether	ion exchange resin makers laboratory workers organic chemical synthesizers polymer makers	UK
	Coal tar & pitch volatiles	artificial stone makers asbestos goods workers	250,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		asphalt workers battery workers boatbuilders brick workers briquette makers brush makers coal tar workers creosoters coke oven workers electrode makers electric equipment makers gas house workers glass blowers insulators linemen miners painters pavers/road workers pipeline workers railroad track workers roofers rubber workers shingle makers water proffers shipyard workers wood preservers	
	Chromium	alloymakers catalyst workers ceramic workers drug makers electroplaters glass colorers nickel workers paint dryer makers porcelain colorers rubber colorers synthetic ink makers	175,000 C
	Radon daughters	uranium miners	5,900 R
Pulmonary Reactions to Man-made Fibers and Miscellaneous Pneumoconioses, Including "Mixed Dust" Pneumoconioses			
Respiratory Effects of Inhaled Toxic Agents	Ammonia	aluminum workers amine workers ammonia workers annealing	3,100,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		bronzers	
		chemical workers	
		coal tar workers	
		coke production	
		compressed gas workers	
		drug manufacturing	
		dye manufacturing	
		electroplating	
		electrotypers	
		explosive manufacturing	
		farming	
		fertilizer manufacturing	
		galvanizing	
		glue making	
		lacquer/latex workers	
		metal extraction	
		metal powder processing	
		mirror silvering	
		paper production	
		perfume manufacturing	
		pesticide manufacturing	
		petroleum refinery workers	
		photographic film makers	
		rayon manufacturing	
		refrigeration workers	
		resin makers	
		rubber workers	
		sewer workers	
		steel workers	
		sugar refiners	
		sulfuric acid manufacturing	
		tanneries	
		transportation workers	
		water treatment	
	Cadmium and Cadmium containing compounds	alloy manufacturing	150,000 H
		auto mechanics	
		battery manufacturing	
		braziers	
		cadmium smelting, refining, processing	
		ceramics	
		copper refining	
		dental amalgam makers	
		electroplating	
		engravers	
		glass making	
		lead refining	
		metalizers	
		paint manufacturing	
		pesticide manufacturing	
		pigment makers	
		solderers	

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		textile printing welders zinc smelting and refining	
	Cadmium Chloride		18,000 R
	Cadmium Oxide		20,000 R
	Cadmium Sulfide		25,000 R
	Chlorine	aerosol propellant makers alkali salt manufacturing aluminum purification bleaching carpet makers chemical manufacturing chlorinated solvent manufacturing chlorine workers disinfectant manufacturing dye manufacturing flour bleachers gold extraction ink manufacturing iron workers laundry workers paper/pulp bleaching pesticide manufacturing petroleum refinery workers plastic manufacturing rayon manufacturing refrigeration workers rubber production sewage treatment silver extraction submarine workers sugar refining tin recovery transportation workers water treatment	75,000 R
	Hydrogen sulfide	barium carbonate makers brewery workers caisson workers cellophane makers citrus root fumigation coke oven workers depilatory makers dye makers farmers fat renderers felt makers fermentation process workers	25,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		fertilizer manufacture fish processing lithographers miners natural gas makers paper pulp makers petroleum/gas refining & processing photo engravers rayon makers sewage treatment plant workers sewer workers silk makers slaughterhouse workers smelting of metallic ore soap makers sugar beet processors sulfuric acid purifiers sulfur makers synthetic fiber makers tannery workers tunnel workers well diggers	
	Mercury (and its compounds)	amalgam makers bactericide manufacturing battery makers boiler makers bronzers cap loaders, percussion caustic sode makers ceramic workers chlorine makers dentists drug makers explosive manufacturing fireworks manufacturing fungicide manufacturing fur preserving/processing gold/silver extraction histology technicians insecticide manufacturing jewelers mercury workers/ mining/refining	150,000 R

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		paint making paper manufacturing pesticide workers photographers tanneries taxidermists thermometer/barometer makers	
	Osmium tetroxide	alloy manufacturing drug manufacturing histology technicians organic chemical synthetization osmium tetroxide production platinum hardening synthetic ammonia manufacturing	3,000 R
	Oxides of Nitrogen Nitric oxide--NO Nitrogen dioxide-- NO ₂	braziers dentists diesel engine maintenance and mechanic workers dye makers fertilizer manufacturing fire fighters food and textile bleachers explosive workers garage workers gas and electric arc welders jewelers medical technicians metal cleaners miners nurses organic chemical synthesizers physicians silo fillers sulfuric acid manufacturing welders	950,000 H
	Oxides of Sulfur Sulfur dioxide--SO ₂ Sulfur trioxide--SO ₃	beet sugar bleachers bleachers boiler water treatment brewery workers diesel engine operators and repair disinfectant makers firemen food bleaching foundry workers fumigant manufacturing	125,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		furnace operators gelatin bleaching glass manufacturing ice making ore smelting paper manufacturing petroleum refining preservative makers protein processing refrigeration workers sodium sulfite manufacturing sulfuric acid manufacturing tanneries thermometer manufacturing (vapor) wine makers wood bleaching	
	Ozone	air treaters arc welding cold storage food preservers industrial waste treatment liquor agers odor controllers oil bleaching organic chemical synthesis sewage treatment textile bleaching water treatment wax bleaching wood aging	750,000 R
	Phosgene	chlorinated compound manufacturing drug manufacturing dye manufacturing firemen isocyanate manufacturing insecticide manufacturing metallurgists organic chemical synthesis phosgene workers plastics production resin manufacturing welding/brazing	6,000 H
	Sulfuric acid	aluminum sulfate synthesis battery manufacturing cellulose workers chemical manufacturing copper sulfate synthesis	200,000 C

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		detergent manufacturing dye manufacturing explosive manufacturing food processing glue making jewelers leather workers metal cleaners paint makers paper production phenol manufacturing	
	Vanadium and Vanadium containing compounds		174,000 R
	Vanadium pentoxide	alloy manufacturing catalysts manufacturing ceramics cleaning of oil fired boilers dye manufacturing ferrovanadium workers glass manufacturing organic chemical synthesization petroleum refining photographic chemical makers printing textile dye workers vanadium smelting, refining, processing welding	3,000 R
	Other Vanadium oxides halides salts of vanadium sulfates vanadates		
Siderosis	Iron and iron oxides	arc welders boiler scalers friction saw operators grinders metal workers mining, milling and transporting iron ores oxyacetylene cutters polishers production and refining of metal and alloys containing iron	1,775,000 R

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		silver finishers stainless steel makers steel foundry workers welding	
Silicate Pneumoconioses	Fibrous Attapulgitic clay (Fuller's earth)	mining and milling of attapulgitic	120,000 H
	Fibrous talc	agricultural chemical manufacturing candy molding ceramics chalk making cosmetics crayon manufacturing dusting powder manufacturing foundries (ferrous and nonferrous) insecticide manufacturing lubricant production mining and milling of talc paint manufacturing paper production pharmaceutical manufacturing pigment production polishing peanuts and rice rubber making roofing material manufacturing salami dusting soap filler addition textile manufacturing white shoe cleaners	1,800,000 H
	Sericite	of no commercial importance; was implicated in the 1930's as a cause of silicosis. Subsequent work has not supported this hypothesis.	UK
	Sillimanite	furnace patching mining and milling of sillimanite porcelain manufacturing for electrical equipment refractories	UK

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
	Wollastonite	cements production ceramics mining and milling of wollastonite plastics manufacturing	67,000 H
	Non-fibrous		
	Bentonite	decolorizing oil production making refractory linings mining and milling of bentonite preparing fine grouting fluids thickening drilling muds water softener production and addition	250,000 H
	Kaolin	bagging and loading of kaolin cements production ceramics paint making paper manufacturing pharmaceutical manufacturing mining and milling of kaolin	1,450,000 H
	Mica	electrical industry insulation production and installation mining and milling of mica or feldspar paint production paper production wallpaper manufacturing	300,000 H
	Portland cement	brick masons bridge building building construction burial vault builders cement plant production (milling) cement workers concrete workers drain tile makers heat insulation makers oil well builders silo builders storage tank builders tunnel builders water pipe makers	500,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
Silico-antimoniosis	Antimony plus Crystalline Silica	Antimony miners	50R
Silicosiderosis	Iron ore Iron oxides plus Crystalline silica	boiler scalers foundry workers iron mining iron and steel workers ochre mining welding	UK
Silicosis	Crystalline silica diatomaceous earth flint granite quartz sand sandstone slate	cement production workers coal mining and milling foundries (ferrous and nonferrous) glass making insulation production and installation metal mining and milling nonmetallic mining and milling plastic manufacturing porcelain production pottery making refractories road working rubber manufacturing sandblasting scouring soap manufacturing stone cutting stone masons tile and clay production tunneling wood filler making	2,300,000 R
Silver Polishers' Lung	Silver plus Iron oxide	jewelers silver polishing silversmiths	13,000 R
Stannosis	Tin Tin oxide	babbitt metal manufacturing brass founding brittania metal making bronze founding dye manufacturing fungicide manufacturing	225,000 H

<i>Disease</i>	<i>Agents</i>	<i>Industry or Occupation</i>	<i>Number</i>
		pewter makers pigment manufacturing plastic manufacturing solder manufacturing textile manufacturing tin miners and millers tin refiners and smelters type metal making	
Trimellitic Anhydride Lung Disease TMA Disease	Trimellitic anhydride	chemical manufacturers dye and pigment manufacturing epoxy resin workers paint manufacture pharmaceutical manufacturing resin manufacturing vinyl plasticizing	11,000 H 10,000 H

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