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Widening Perspectives of Occupational Lung Disease[1]

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It is something of a paradox that the basic concepts which helped establish much of our current knowledge concerning occupational and environmental lung disease are now often found to be inadequate and occasionally even inappropriate or misleading.

At the turn of the century, there was general belief that dust, fumes, and vapors might cause lung damage. Agricola had written almost four hundred years before of lung disease in Saxony mines (1) [the very mines which, in our times, yielded the first knowledge of radiation lung cancer (101)], and the grinding shops of nineteenth century Britain demonstrably shortened the lives of their workers. Yet, little could be said definitely about this. Many dust-exposed workers—farm laborers, for example—lived long lives, while others, even with lungs blackened by dust in Scottish coal mines, suffered no evident ill health (84). Moreover, the widely prevalent lung disease, tuberculosis, was not seen to be related to dust or fumes; its frequent presence often confounded and overwhelmed other lung disease which might be present.

It is, therefore, to the considerable credit of our predecessors that they were able to make order of this contradictory and diffuse situation. If one contribution can be said to have provided clarity and definition it may be Collis' brilliant Milroy Lectury of 1916 (22), in which he established for the first time that a specific dust particle—crystalline silica (SiO_2)—had a biologically unique effect. He did this, incidentally, by using what would now be labeled an epidemiological approach—workers exposed to dusts with high concentrations of free silica (as, quartz) died much more frequently of tuberculosis than did workers exposed to dusts of other composition. Demonstrating this effect, he gave new meaning to the word "pneumoconiosis," introduced 50 years before (144). After Collis, it was no longer a specific disease but rather a generic term which covered a variety of dust diseases of the lung—and opened the way for its compartmentalization into many categories (silicosis, asbestosis, talcosis, beryllium lung disease, coal workers' pneumoconiosis, aluminosis, and others), all related by the presence of pulmonary reaction (primarily fibrosis) to dust in the lung parenchyma.

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Two methodological perspectives seemed to flow from this discovery. In their time, they were reasonable. First, was the stricture that there should be a one cause/one effect relationship; indeed, this seemed a good biological principle and consonant with observations then being rapidly made in infectious disease. Second, on the other side of the coin, specific lung changes were sought and often found after exposure to specific substances. When it was finally agreed, for example, that asbestos (without free silica) could cause lung disease (25), it was logical to find that the fibrosis it produced was diffuse rather than nodular (40).

Moreover, the approach has in many ways been a productive one. With it, we have been able to determine that some metal particles as iron or tin (103) produce little pulmonary reaction. The sometimes serious consequences of beryllium exposure were found early although, at least in the United States, we were laggard in acting upon this recognition (47), in part because animal studies did not show an expected specific effect. Tungsten carbide, talc, nonfibrous silicates as kaolin (31), aluminum (41), titanium (77), and others were all discovered to have their own pathogenicity. Even today, it makes good sense to isolate a substance in the human environment, so far as is possible, to study its effects, and this technique is almost universally used in animal studies.

Nevertheless, however well this concept has served us to this point, there has been a growing realization that these methods are incomplete and restrictive (116). As a result, wider perspectives have emerged, especially in the last ten years.

Mixed dust exposures. While it makes good sense, for purposes of identification and definition, to study isolated exposures, in industrial circumstances these are more often the exception than the rule. In mining, for example, ores are complex with a variety of minerals, and the dusts produced during extraction and beneficiation reflect this diversity (66). Moreover, under some circumstances, the presence of some minerals may potentiate, or diminish, the effects of others; their concurrence need not be biologically neutral. Thus, while "pure" graphite can produce disease, its contamination with silica may add to the fibrogenic response (96). Similar effects are noted with coal dust and provide at least part of the explanation for the differences seen with anthracite and bituminous coal mining (92).

Mixed dust exposures are also common in industrial practice. Insulation workers, for example, are called "asbestos workers" (indeed, they belong to the "Asbestos Workers Union"), yet the materials with which they work often contain only fractional amounts of asbestos and sometimes no asbestos at all (127). Merewether was aware of this when, 40 years ago, he sought to ascertain the extent of the risk associated with the industrial use of asbestos (86). He sought out a "pure" asbestos trade, the manufacture of asbestos textiles. While this did provide clear information concerning the fibrogenic potential of asbestos, it also attracted scientific and medical attention to what has turned out to be a relatively uncommon use of asbestos, and several decades went by before concern was redirected to less well-defined but, in terms of workmen

involved, much more important uses, such as those in the construction industry (117,118).

The frequency of mixed dust exposures in industrial practice makes it unwise to expect that "classical" X ray patterns will regularly be seen on roentgenograms in all cases. While silicosis will often show the expected nodular infiltrations, linear and reticular shadows are also commonly seen. This is also true in coal workers' pneumoconiosis (95), and among iron miners (108), while in asbestosis, small nodular shadows may complicate the linear reticular pattern of diffuse interstitial fibrosis (11). The appreciation of this diversity has recently led to the modification of the International Classification of Roentgenographic Appearances of Pneumoconiosis. Culminating an 8-year review of the problem by groups of experts, a new Classification was agreed upon in 1971 (57), and allows the description of the complexity of X ray changes that are commonly seen.

Multiple factors in occupational lung disease. Just as complex dust exposures are the rule, it has recently become apparent that there is a comparable complexity in the total environment of the worker which must be considered. This includes both the occupational and nonoccupational setting.

Of the two, it appears at the moment that personal factors have the greatest influence. Living conditions and style of life may play a role (54,55,105); their exact effect is not fully clear. Cigarette smoking, on the other hand, has great influence.

The first well-defined report on the powerful effect of smoking on industrial lung disease was that of Sluis-Cremer (125). He demonstrated that the incidence of bronchitis among gold miners depended upon whether or not they also smoked cigarettes; if they didn't, they had no greater risk than similar adult males in the same community. On occasion, it is even difficult to differentiate an effect of an adverse occupational environment, as in SO_2-plagued steel mills, because of the overriding influence of cigarette smoking (74). The same difficulty may be found in studying the influence of community air pollution (46), or industrial lung disease in the coke industry (141).

In some circumstances, the cigarette smoking effect may be additive or may exaggerate or potentiate the influence of the occupational environment; this is seen in byssinosis (85) and in respiratory disease among coal miners (27).

Recently, it has even been found that the existence of radiologically evident pulmonary fibrosis following asbestos exposure has such an association (142). With similar duration of work exposure, the smokers tend to have more radiological evidence of parenchymal fibrosis. One factor may have been the tendency for cigarette smoking itself to result in some pulmonary fibrosis (4); other mechanisms have been suggested.

The metabolic status of the individual may be important: the subject has hardly begun to be studied (24). While hints have been available for some time [as, possible effects of concomitant infection (6,21)], the recent identification of the importance of $alpha_1$-antitrypsin deficiency in the pathogenesis of some cases of emphysema (36,134) has attracted much-needed attention to this field of research. Indeed, such genetic defects may eventually explain

unusual syndromes in occupational lung disease and some of the individual variations in response to apparently identical occupational exposures which perplex us. Similarly, immunological (including auto-immune) response to pneumoconiotic dusts may explain not only such basic phenomena as the resulting fibrosis (16,137) but more esoteric observations including the occurrence of Goodpasture's syndrome following the inhalation of industrial solvents (10,32).

Physical interactions may also be significant. Thus, inert particles (as, carbon) may absorb and potentiate noxious gases (SO_x, NO_x) (12) or carcinogenic materials (88, 109); little is known about interactions with physical environments (heat, cold, radiation), although clinical suspicion exists that these may be important. There may be no such thing as an "inert dust," innocuous in all circumstances. The total dust burden of the lung in respiratory disease among coal miners, for example, plays a pathogenetic role (106), perhaps by mechanical effect on lymphatic and bronchial clearance; even nepheline inhalation, if extensive enough, can produce fatal lung disease (7).

Individual variations as a result of genetic, immunological, and metabolic factors have been mentioned. Other causes are still obscure and may include physiological factors associated with age and nutrition (59). The spectrum of potential interactions is wide and provides fertile fields for critically needed research (71), since it may turn out that much occupational lung disease—and environmental lung disease, in general—would not occur except with the additive or even multiplicative effect of two or more agents. This has important useful connotations since, in some circumstances, it may be practical to focus on the elimination or control of one or another agent, least difficult to attempt. If there be a *chain* of pathogenetic events between initiation and clinical disease, all links in this chain may not be equally strong or inaccessible. Identification of one *weak link* may allow us to interrupt an otherwise inexorable progression of disease. Two initial proposals can be mentioned: the screening of new employees for $alpha_1$-antitrypsin deficiency and for cigarette smoking, before their hiring for trades which include risk of emphysema or pneumoconiosis (134). One could argue, correctly, that these industries should provide work environment without any risk. From a practical point of view, however, the best-controlled work environment is unlikely not to have some trace of the noxious agent, hazardous only to the specially susceptible individual.

Compound and variable substances. Not infrequently, industrial exposures occur to multiple agents naturally. This is almost invariably the case with mineral dusts; the ores are complex mixtures of minerals, often varying from seam to seam. The extraction and beneficiation processes rarely result in uncontaminated, unique, single substances, except perhaps when laboratory grades are sought. Exposures, usually, are to more than one mineral component, the proportions varying with each step from mine to end use of the material. It is thus inadequate to speak of "exposure to coal dust" or to "asbestos" or to "talc." A miner may inhale varying amounts of quartz while quarrying tin (103), mica (52), or talc (124), and "rock dust" exposure frequently accompanies coal extraction. It is instructive to remember that the pathogenetic

properties of coal dust per se were first isolated by demonstrating disease in coal handlers in transportation, away from the mines (23). It is likely that the spectrum of findings among coal miners relates at least to some extent to variations both in the rank of coal mined and its silica content (91), and disease with graphite also reflects contributions from both its carbon and silica content (96). Lung disease with cement may also reflect variability of the dust, and there has long been concern with the foundry environment (83). Failure to appreciate the potential effect of such admixture long delayed the recognition of the possible fibrogenic effect of bentonite (99) and hematite mining (37,132), while diatomaceous earth may give little trouble—unless its amorphous silica is altered to crystalline tridymite or cristobalite by calcining. Shaver's Disease (123), too, has been studied not only in relation to aluminum ore, but to particle size and silica content, and hard-metal pneumoconiosis (19) is so named because of the varying materials involved in its causation.

The possibility of complex agents exists even in industrial processes and agents. Several recent examples will point the problem. Abrasive soap mixtures may contain fine sand mixed with either acid (*viz.* oxalic) or with alkalies, potentially altering the effect of the fine silica in the ensuing abrasive soap pneumoconiosis. Printing pressmen may suffer lung disease—the matter is now under study—and both carbon black and oil mists in their environment are being investigated (72,89,94). Respiratory disease as a result of detergent enzyme exposure is another instance of exposure to variable substances (9,38). [To complicate the matter further, the particular substances under consideration may vary in their effect not only by virtue of the chemical and physical nature, but also because of particle size and shape. Long known for particles of silica, it has recently been suggested that it may be true for some fibers as well, as fibrous glass (131).]

Multiple effects of single agents. The obverse of the multiple factor coin is the fact that some agents, in and of themselves, may have more than one biological effect. *Asbestos* can produce pulmonary fibrosis *and* cancer (vide infra). Both aluminum dust and diatomaceous earth may result in fibrosis and spontaneous pneumothorax. There is some evidence that cotton workers have not only reversible bronchial physiological effects but may have some "nonspecific" anatomical changes as well, and farmer's lung, as other varieties of extrinsic allergic alveolitis, may be marked both by bronchial disease and notable pulmonary fibrosis (113). Radiation can produce both fibrosis as well as cancer (63), manganese may produce Parkinsonism as well as pneumonitis (128), while caisson workers are subject to lung as well as bone changes (81).

Nonfibrotic pulmonary disease. The recognition of the importance of occupational factors in pulmonary disease other than that characterized by fibrosis was delayed, possibly by the fact that the findings resembled those which are noted in nonoccupational settings, as bronchitis and emphysema (53,107)[2]. This difficulty may be a real one, since tissues can respond to a variety of insults in a limited number of ways (39). However, careful occupational

[2] The importance of the problem may be appreciated by recognition that chronic bronchitis and emphysema are currently more important than silicosis among white gold miners in South Africa (20).

history, especially that detailing work exposures two, three, or more decades before, can help identify occupational factors, and we may anticipate that, so assisted, we will learn much more about specificity of "nonspecific" syndromes than we now appreciate. This is very likely to be the case with respiratory disease among cotton workers, now that its importance in the United States has been recognized (13).

Bronchial changes—functional or structural—have been little studied, although they seemingly underlie much disability in such conditions as byssinosis, bronchitis with physical and chemical agents, detergent enzyme exposure, and the variety of syndromes (largely in response to exposure to organic materials) gathered under the rubric of extrinsic allergic alveolitis (82,97). These include such increasingly common categories as cork (suberosis) (5) and farmer's lung (29,43), as well as esoteric varieties, as paprika-splitter's, or smallpox-handler's lung, or maple-bark disease, or that associated with redwood dust (sequoiosis). Sometimes, particles of the offending agent may be retained in the lung [furrier's lung (100)]; other times, the exposure is evanescent. Recently, particular attention has been paid to small-airway disease in occupational lung syndromes, both those found with organic materials, such as cotton dust, as well as with pneumoconiotic dusts, such as asbestos or coal. This is likely to prove a very fertile field for research (78,104).

Acute occupational lung disease, again largely resulting from bronchial reactions, may be found in metal fume fever and with isocyanates (114). Usually short-lived in the former, they may be life-threatening with the latter, and their recognition important, since the affected individuals often should best avoid further exposure. Death may also follow paraquat poisoning; here, progressive fibroblastic alveolitis is at fault (26).

Uncommon pulmonary abnormalities observed in an occupational environment include cystic changes occuring following hyperbaric exposures, as with caisson disease. Not infrequently, the roentgenological appearance is complicated by concurrent pulmonary fibrosis, since the workers involved often have pneumoconiotic dust exposure as well, in tunnel and caisson work.

Occupational lung cancer. The possibility that toxic inhalants in the workplace could lead to lung cancer has long been considered, especially with regard to silicosis. There was a general consensus, however, that the incidence of this neoplasm was not increased in such circumstances; indeed, the likelihood of its occurrence among coal miners was found to be less than expected. Against this background, data suggested an increased incidence among hematite miners (14,37).

Within the past two decades, the clear demonstration that lung cancer and other intrathoracic neoplasms could occur in excess as a result of occupational exposures has turned the situation around. With some exposures, a neoplastic hazard now outweighs other pathological effects both in frequency and importance. This is true, for example, with fluoride mining (28), asbestos (30,117,121), uranium mining (75), nickel smelting (44,133), talc mining and milling (61), and chromate production (64). The forecast inherent in the 1879 observations (51) in Schneeberg have been borne out; perhaps this hazard underlay Agricola's description of pulmonary disease in the same mines almost four centuries before (1,56).

Even coal mining is no longer without suspicion (90), and recent observations suggest that the question needs to be restudied. In such investigations, the possibility of multiple factor etiology will have to be taken into account, especially the potentiating effect of dust exposures on the lung cancer risk associated with cigarette smoking (75,121).

A special circumstance of particular interest in recent years has been the occurrence of pleural neoplasms associated with occupational dust exposure (asbestos). Pleural mesothelioma has until recently been extraordinarily rare, with only infrequent cases being seen since the classic modern description of the tumor in 1931 (62). Its occurrence with asbestos exposure (139)—coupled with the wide use of this material—has made this a common problem in occupational lung disease practice (119). In several cohorts of asbestos workers studied by us, more than 5% of all deaths were the result of mesothelioma, $\frac{1}{3}$ pleural and $\frac{2}{3}$ peritoneal (122). Two features of this complication of asbestos exposure have resulted in much concern. First, spreading rapidly over the entire pleural surface, it has proven invariably fatal (Fig. 1). Second, it may occur with no radiological evidence at all of asbestosis, indicating that the extent of exposure necessary for the development of asbestosis might be quite different from that needed to initiate mesothelioma, with very much less dust producing the tumor. As a practical consequence, dust control measures, designed to keep exposures low enough to prevent asbestosis, might be inadequate to prevent pulmonary and pleural neoplasms.

Pleural disease. Pleural changes as an important accompaniment of occupational lung disease has been recognized for more than three decades but have gained prominence only within the recent past. A variety of conditions may be seen, ranging from spontaneous pneumothorax complicating diatomaceous earth pneumoconiosis or aluminosis to the fibrotic pleural plaques, diffuse pleural thickening and pleural calcification of asbestosis, talcosis, and mica pneumoconiosis (115,126). The importance of this appreciation is emphasized by the recent inclusion of major categories for pleural disease in the revised classification of radiographs of pneumoconiosis of the International Labor Office (57).

From the diagnostic and therapeutic points of view, also, this emphasis is well deserved. Pleural calcification can provide a most valuable "marker" for prior asbestos exposure (60), and fibrotic pleural plaques, especially on the diaphragm, can serve the same purpose. Such stigmata may be very limited in extent, often only a tiny fleck of calcification on the costal or diaphragmatic pleura. When fibrosis is diffuse and extensive, it may occasionally cause severe respiratory insufficiency (Figs. 2 and 3). If, in such circumstances, the pulmonary parenchyma is not unduly compromised, pleural decortication can be an effective therapeutic measure. Active intervention for the management of spontaneous pneumothorax in patients with diatomaceous earth pneumoconiosis or aluminosis (Fig. 4) can also be life-saving, especially since spontaneous pneumothorax is an important cause of death among workers with extensive diatomaceous earth pneumoconiosis.

Reference has been made to neoplastic pleural complications associated with occupational asbestos exposure. This has also been observed among talc

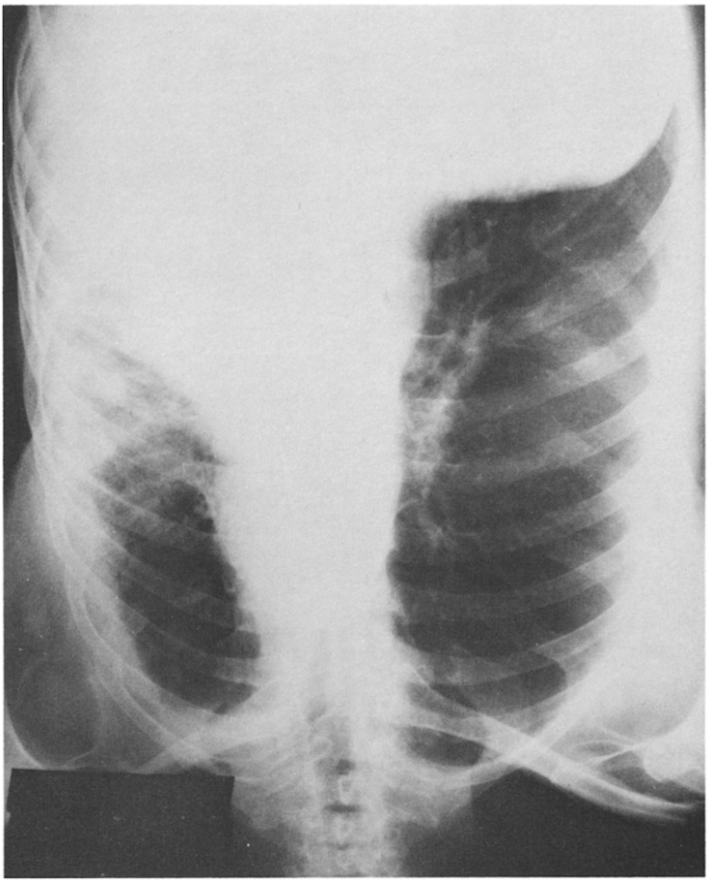

FIG. 1. Pleural mesothelioma in an asbestos insulation worker. Tumor characteristically envelopes entire lung, including costal, mediastinal, and diaphragmatic aspects. Extent has precluded successful surgical approach. Chest X ray a year before had shown no evident disease, and right hemithorax of this film still demonstrates no asbestosis. Mesothelioma may occur as a result of exposure insufficient to produce pulmonary fibrosis (asbestosis).

workers. Among them, too, mesothelioma may be the result of asbestos exposure since asbestos contamination of the talc ores is a common occurrence. Experimentally, a variety of dusts, including fibrous glass, produce mesothelioma (131), and the possibility that these might do so following occupational exposures is being studied.

Extrapulmonary effects of occupational pulmonary disease. It has long been known that there can be extrapulmonary dissemination of inhaled dusts and chemicals. Pulmonary deposition of particles is largely of a size smaller than 5 μm diam, well within the capacity of tissue capillaries carrying 7-μm red blood cells. Macrophage ingestion and transport is an important mechanism. Further, systematic effects, especially those associated with immunological changes (16, 137), need not depend on lymphohemotogenous dissemination.

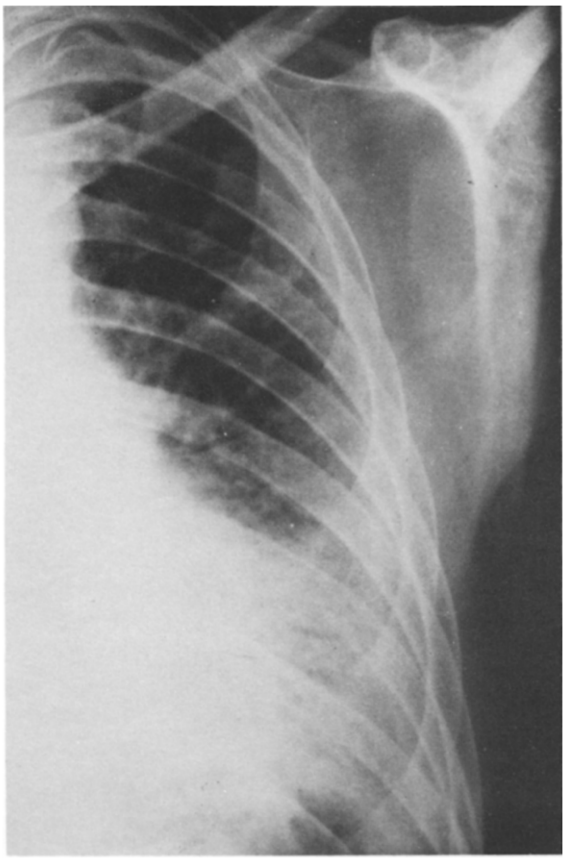

FIG. 2. Diffuse pleural fibrosis of asbestosis may totally encase the lung as a cuirass.

A number of significant observations have been made in the recent past, and it is highly likely that this will be a fruitful area for investigation and study in the immediate future. The spectrum of potential changes can be appreciated by a brief recounting of some of these observations. Caplan has described the syndrome of pneumoconiosis and rheumatoid arthritis (17,42), and this has been extended by the observation of the presence of rheumatoid factor in the serum of many individuals with pneumoconiosis but without evidence of arthritis (98,136). These observations have been recorded with coal workers pneumoconiosis, asbestosis, and silicosis, for example.

Extrathoracic neoplasms are also now known to occur in association with occupational dust exposure. These include gastrointestinal neoplasms (121,122) with asbestos exposure, and possibly with metal mining (140), coal mining (34,80) and coke oven exposure in steel mills (73). Peritoneal mesothelioma has already been mentioned; it is a common and serious complication of asbestos exposure (35,122). The pathogenetic mechanisms which underlie these neoplastic complications have not been established. It is likely that the

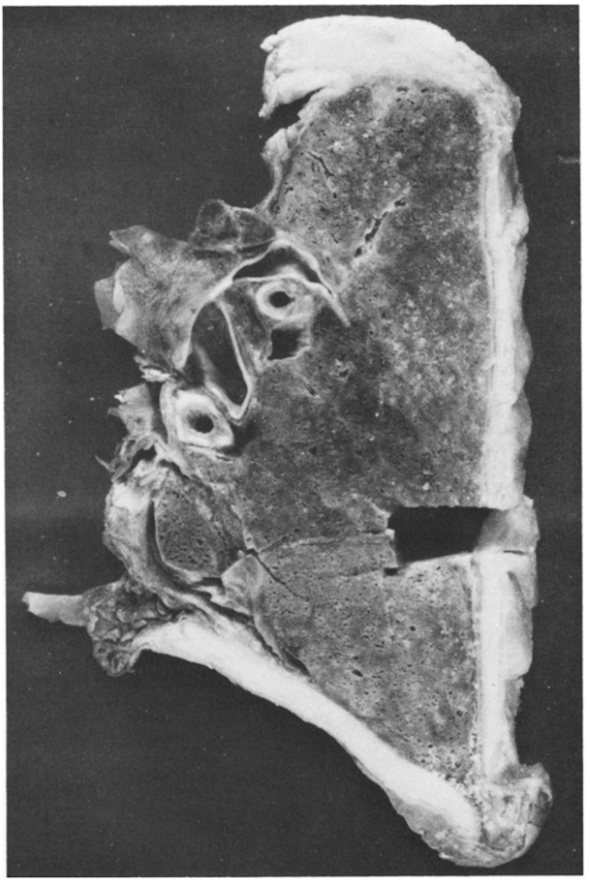

FIG. 3. Death occurred of pulmonary insufficiency. Function was impaired both by the diffuse interstitial parenchymal fibrosis, also present, and the restrictive effect of the pleural thickening. Generally, parenchymal disease has the more important bearing on the outcome.

physical presence of inorganic microparticles plays an important part, dissemination occurring either through the gastrointestinal tract (Fig. 5) or by lymphohematogenous dissemination (Fig. 6). In the former, the phenomenon of persorption may have pathogenetic significance (138).

The demonstration that the surfaces of a number of inorganic particles, such as fibrous glass and asbestos, may alter Hageman factor metabolism (102) similarly opens a wide area for investigation. A surface effect may be responsible for the hemolytic properties in *in vitro* red cell systems of a large variety of inorganic particles of occupational importance. This, too, is now actively being investigated (112).

Quantity and quality. It has long been well understood that there is no "all-or-none" law applicable to occupational lung disease but that the likelihood of clinical change of consequence depends upon the level of exposure, modified by such variants as total duration of exposure and duration from

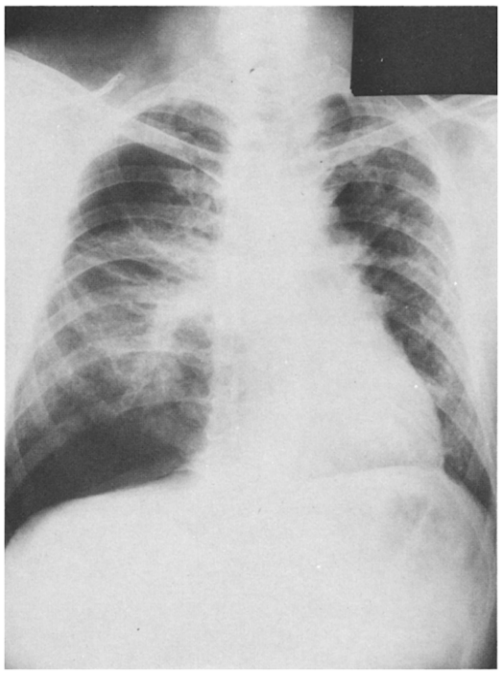

FIG. 4. Spontaneous pneumothorax in patient with aluminosis. This may be life-threatening complication. This complication may also occur in the course of diatomaceous earth pneumoconiosis, with the same significance.

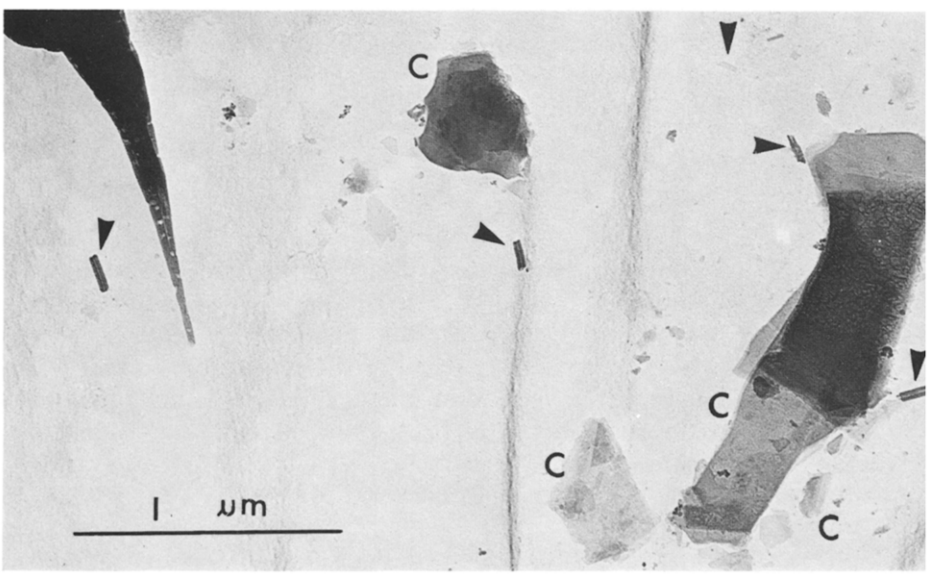

FIG. 5. Transmission electron micrograph of colonic tissue obtained from an asbestos worker. Small fibrils of chrysotile (arrows) and fragments of clay minerals (marked C) are observed. Magnification as marked.

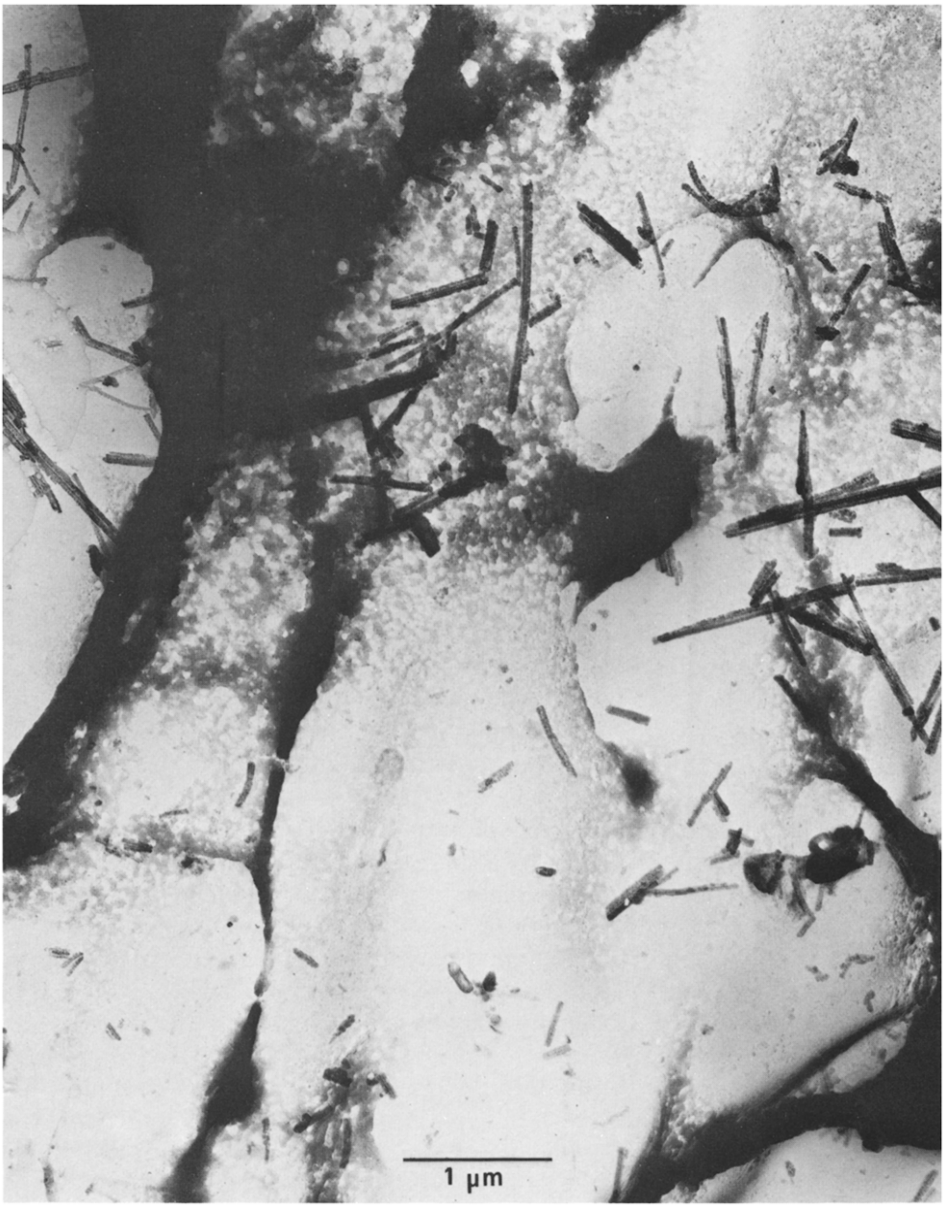

FIG. 6. Chrysotile fibrils in liver of asbestos factory worker, demonstrating lymphohematongenous dissemination. The unit fibrils are 200–400 Å in diameter and cannot be seen by optical microscopy. Electron micrograph, ×10,000.

onset of exposure (see below). Within limits, such dose-disease response relationships are consistent and underlie the concept of Threshold Limit Values (3).

In some circumstances, however, the relationship is hardly straightline,

with few or no qualitative effects seen until one reaches a very marked quantitative shift. Quantity becomes associated with qualitative differences. One reason for this is that two different physiological and pathogenetic processes are involved. Clearance mechanisms ordinarily may be entirely adequate to prevent undue accumulations of dust, whatever their fibrogenic potential. When such clearance mechanisms are overwhelmed, however, the inhaled dusts may then produce significant changes. Such mechanisms have been invoked in coal workers' pneumoconiosis, nepheline lung, graphite pneumoconiosis, as well as with instances of lung disease with kaolin or talc exposures. Carbon black, increasingly used in industry, may also have such an effect.

An analogous situation exists with exposures to irritating fumes and vapors. Here, the repair processes of bronchial and alveolar tissues can be outstripped.

A world of fine particles (135). The past two decades have seen considerable interaction between conceptual advances in biological research and the availability of new analytical instruments and techniques. This is true in the field of pneumoconiosis as well. Until recently, histopathological studies have been limited by the power of resolution of the optical microscope, capable of demonstrating particles 0.5–5.0 μm or larger. Inability to detect particles smaller than 0.5 μm was not considered a serious limitation, since aerodynamic theory predicted that particles smaller in effective diameter were unlikely to be deposited in the lung, even if they should be present in the inspired air. It is now realized that this is an inadequate approach, and the availability of the electron microscope offers an exceedingly important new direction for research, with relevance not only to industrial lung disease, but to atmospheric pollution, as well. It may turn out that particles visible by light microscopy play a relatively minor role in human disease. Submicron particles almost invariably accompany them and may have much greater pathogenetic significance; for a given mass their surface area is very much greater. The subject is largely unstudied. In many instances, optically visible particles are absent, yet disease occurs with the presence of particles in the Angstrom range (87). New techniques allow not only the demonstration of such particles, but their unique identification as well (65–69). And recent aerodynamic considerations indicate that a very significant proportion of submicron fibers are likely to be deposited in the lung (Figs. 7–8) (50).

Community effects associated with occupational lung disease. It was not until the serious consequences of neighborhood beryllium disease were clarified that the important potential of community exposure to pneumoconiotic dusts (and other industrial materials) was widely recognized (18,33). In the recent past, there has been growing interest in this problem, ranging from studies concerning the health effects on children of cement and similar dusts in Romania (76) and neighborhood byssinosis in Egypt (8) to environmental asbestos disease (120). The latter has been perhaps best studied and provides ample evidence of the growing potential importance of this accompaniment of occupational lung disease.

The first hint that asbestos dust derived from industrial use of the material

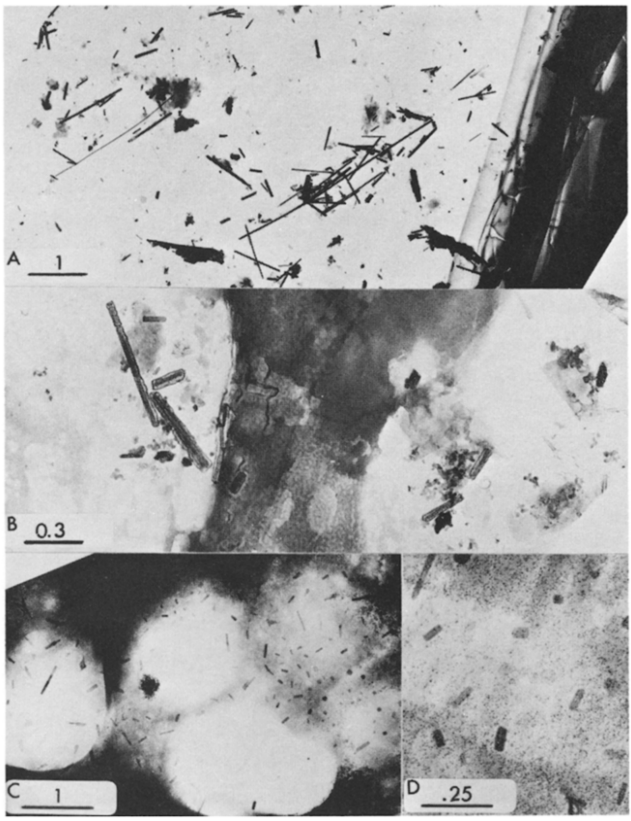

FIG. 7. Transmission electron micrographs of lung tissue from individuals exposed to asbestos dust. (A) Talc dust exposure. Chrysotile asbestos fibrils found throughout lung tissue. (B) Worker indirectly exposed to asbestos. These fibrils would not be detected by optical microscopy. (C) Clinical diagnosis, interstitial fibrosis of unknown etiology. Large numbers of chrysotile fibrils indicates probable intimate exposure. History not available. (D) High magnification of C. *Length* approximately 1500 Å.

might be of importance came many years ago when Haddow (45) found asbestos bodies in the lungs of a person living close by an asbestos factory. More recently, the finding of mesothelioma among individuals whose only contact with asbestos was by virtue of residence within the household of an asbestos worker or by living within a half mile of an asbestos plant, has attracted much attention (93,139). The practical importance of this question has been emphasized in the past year by the recommendation by the Occupational Safety and Health Administration of the Department of Labor that, in specific circumstances, precautions are required to prevent household contamination from dust carried on work clothes or shoes (130). Similarly, the Environmental Protection Agency is now considering appropriate regulations to prevent environmental contamination from asbestos mines, mills, and factories, as well as from other industrial uses of asbestos.

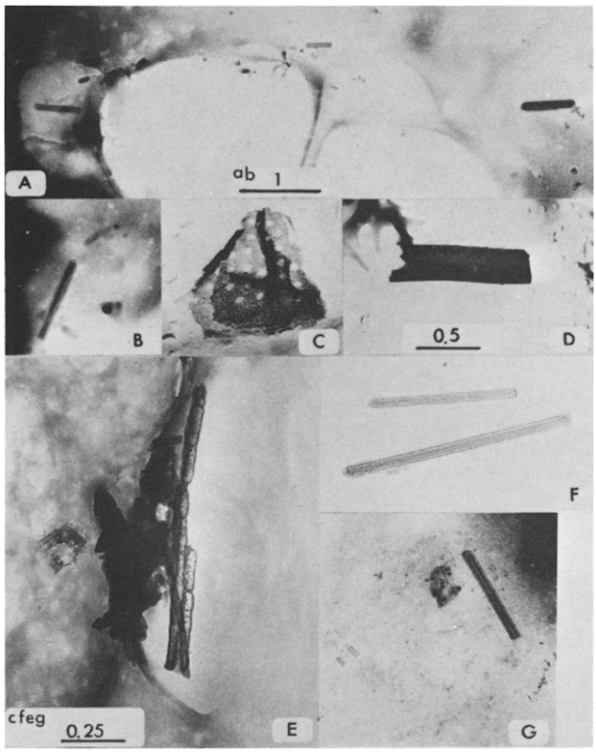

FIG. 8. Transmission electron micrographs of extrapulmonary tissues. A–D demonstrate particles observed in the pancreatic tissue of an asbestos worker with a primary tumor of the pancreas: (A and B) chrysotile asbestos fibrils, (C) diatomaceous earth fragments, (D) fibrous glass fragments, and (E) particles in tissue of ovary in which a malignant neoplasm was present. (F and G) Chrysotile asbestos fibrils obtained from the peritoneal fluids of an asbestos worker with peritoneal mesothelioma (confirmed at autopsy).

Epidemiological considerations. In general, there is a long-lapsed period between onset of exposure to occupational hazards and the appearance of clinical evidence of occupational lung disease. Sometimes, brief exposures, if followed by a long enough lag period, are sufficient to produce serious disease. In such instances, residence time in the lung is more important than the duration of exposure perhaps decades before (See below). There are exceptions, of course, especially with gases, fumes, and vapors causing acute disease; relatively rapid initiation of pneumoconiosis may also occur, as in acute silicosis (15) or abrasive soap pneumoconiosis. Beryllium disease may be associated with both acute bronchitic changes as well as long term fibrosis (79). Excessive exposure to calcined diatomaceous earth may also run a fairly short course, and we have seen death of pulmonary insufficiency following exposure of sand blasters to high concentrations of quartz or of asbestos factory workers to similar exposures to asbestos, in less than ten years. Even neoplasms of the upper respiratory tract may occur, with at least one occupational substance, bis(chloromethyl)ether, in a relatively few years (70).

Nevertheless, by and large, decades usually elapse between onset of exposure and evidence of significant disease, especially disabling disease. Appropriate data are now available for asbestos lung cancer, for example, and it has been found (122) that increased risk for both this neoplasm and pulmonary mesothelioma is usually not evident much before 15 years from onset of exposure, with the greatest excess being seen 25–40 years from onset. This long lag period sets important constraints on epidemiological investigations, since the passage of time often diffuses and obscures cause-and-effect relationships. Frequently, the worker is no longer employed at the site of original exposure and, equally often, not even in the same industry. The exposures themselves may have changed quantitatively or qualitatively, or have been eliminated.

It is possible to mount appropriate studies; they must, however, be carefully drawn, cover an adequate time period, and be meticulously, diligently, and completely carried out.

Many of the lung changes which occur as a result of exposure to occupational agents are seen in other circumstances as well—bronchitis, emphysema, lung cancer, diffuse interstitial fibrosis, hypersensitivity lung disease. They are rarely unique to the exposure, although pleural calcification and progressive massive fibrosis approach that status. Definition of a risk of occupational agents depends, then, on the finding that such diseases are present more frequently among the occupationally exposed. This is no hardship when the excess risk is very great, but if the excess risk is modest, as with perhaps only twofold or threefold increase, its demonstration may be much more difficult and will involve the study of considerably larger populations of workers. When we add to this overriding consideration inclusion of such other variables as age specificity, relation to duration from onset or variable levels of exposure, secular changes in the spontaneous occurrence of the disease in control populations, or possible effects of concomitant or competing factors, one can appreciate the epidemiological insecurities in the study of cause-and-effect relationships associated with some occupational exposures. Of considerable value has been the demonstration in recent years that investigation of large exposed populations is entirely feasible.

The detection of increased risks among employed populations can provide an important bonus. Many employed groups are exposed in intimate circumstances and, at fairly high concentrations, to agents to which the general population is also exposed, albeit much more diffusely and at much lower concentrations. The experiences of such occupational groups can then often tell us whether or not the suspect agent might be a general environmental hazard, as well. If an occupational group exposed at high levels shows a cancer risk, it need not mean that the population at large also has risk, but it would at least give some caution and provide direction to prevent the occupational hazard from becoming a general environmental one. On the other hand, if the heavily exposed occupational group has no evidence of excess disease hazard, it would make it much less likely that the general community is at risk.

Treatment. In general, treatment for lung disease resulting from exposure to adverse occupational environments follows the precepts and techniques used

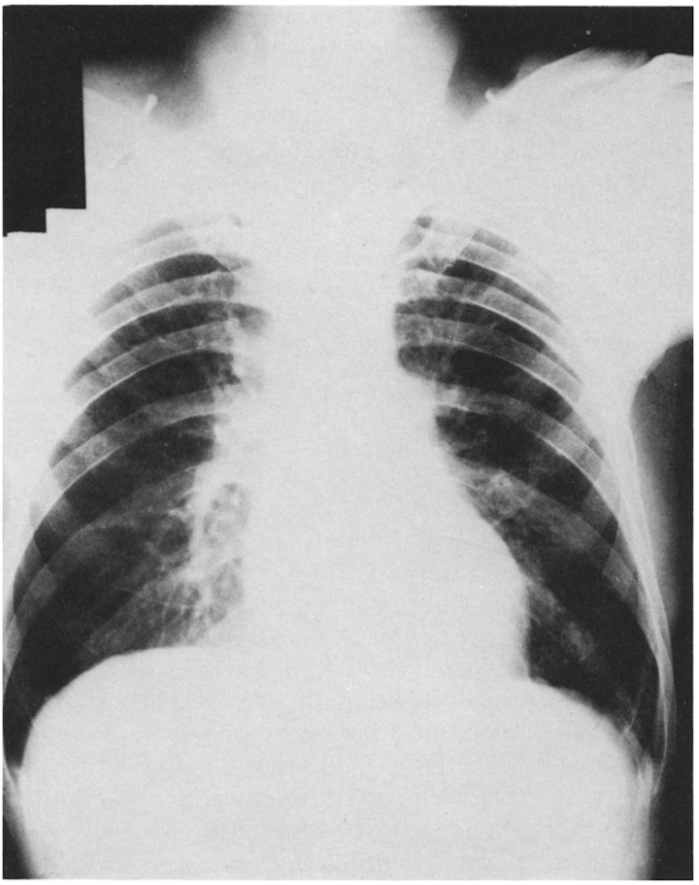

FIG. 9. Routine chest X ray, August 3, 1951, shows no abnormality.

in their treatment on other occasions. There is one important addition: Since these are man-made diseases, prevention is possible and must be sought, with avoidance of exposure by elimination of the offending agent, isolation of the process, substitution of materials and processes, respiratory protective devices, etc.

Until recently, there has been little hope of ameliorating or reversing the effects of occupational lung disease or preventing its progression once it had been initiated, even after removal from additional exposure. New leads, however, have appeared and suggest the possibility that additional approaches are feasible. Schlipköter (110) has demonstrated that at least one substance (polyvinylpyridine-*N*-oxide) can prevent silica fibrogenesis in the experimental animal even when administered after dust exposure. It is possible that the polymer exerts an intracellular protective effect (2). There are observations to suggest that a variety of substances can effect the biological properties of pathogenic dusts, at least in *in vitro* test systems (48,49,111). Whether they

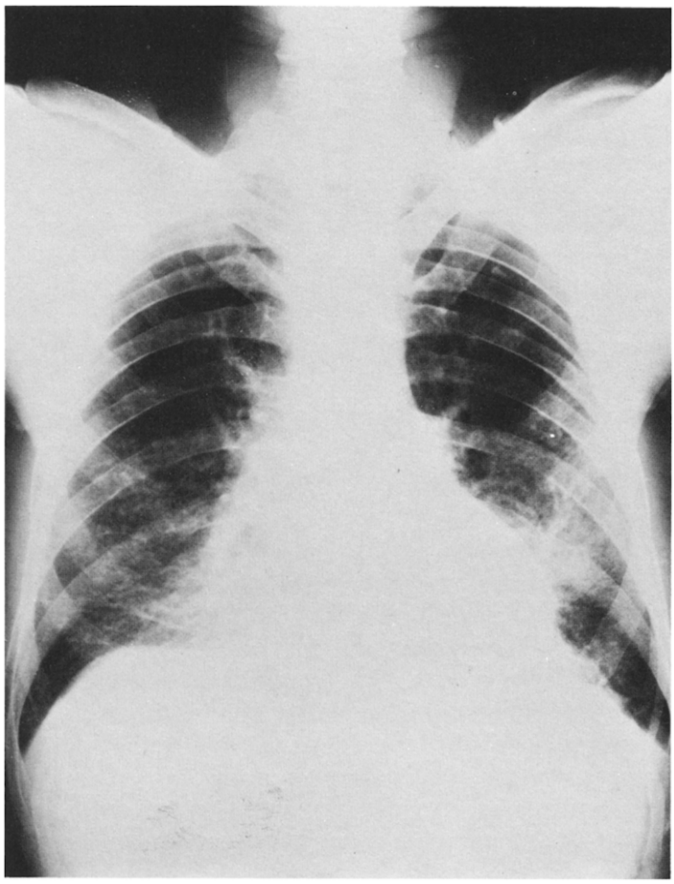

FIG. 10. Film, July 2, 1958. Shortness of breath had been noted. Patient denied any unusual occupational exposures.

will also do this *in vivo* is not yet known, although the use of polyvinylpyridine-*N*-oxide is now being studied for the treatment of coal workers' pneumoconiosis (143) and in experimental silicosis in baboons (129).

Delayed appearance of occupational lung disease. Four factors largely determine the extent and severity of occupational lung disease: the nature of the agent, the duration and intensity of exposure, and the time from onset of exposure. The last is particularly important in dust diseases, since exposure of the lung tissue is by no means synonymous with exposure of the individual. Intense exposure to pathogenic dusts by a worker for one day, one week, or one month may provide sufficient lung burden to result, years later, in disease, both fibrotic and/or neoplastic. In the interval, the retained dust, incompletely eliminated or altered, exerts its effect on cellular elements with which it is in contact, often injuring a series of phagocytic cells, each unable to metabolize the inorganic particle and succumbing in the process.

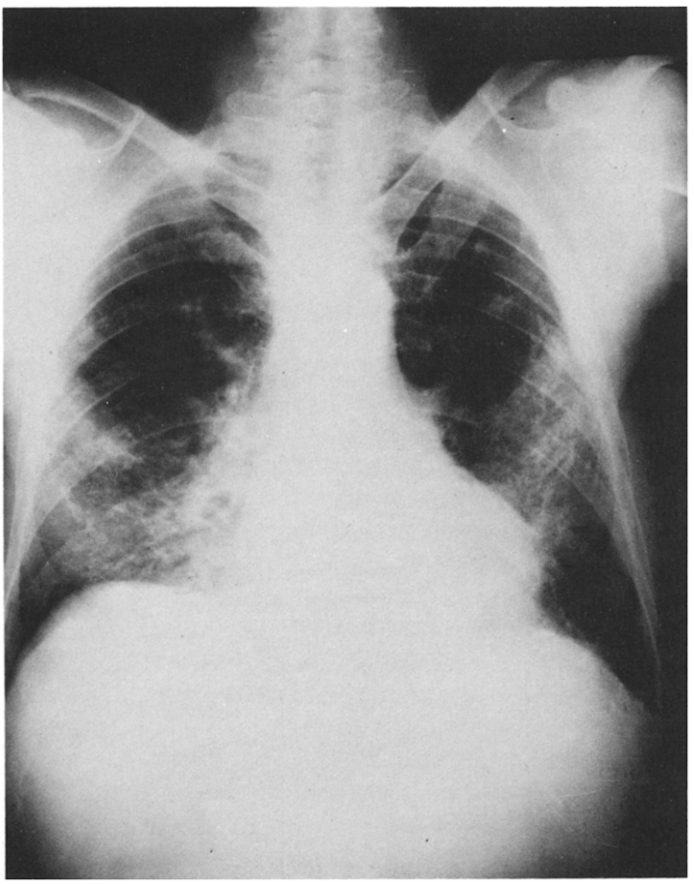

FIG. 11. November 11, 1968. Lower lobe fibrosis and pleural calcification made diagnosis of asbestosis very likely. At this time, patient remembered having worked as an asbestos weaver in a brake lining plant for six months in 1934.

Even when the duration of exposure is identical with the duration from onset of exposure (i.e., continuous employment), the biological effects of the lung dust burden of a worker are a composite. The first dust inhaled, let us say, thirty years before, has the effect of a thirty-year-in-residence dust, capping the inverted pyramid of its decades of damage. Dust inhaled 20 years before is having a twenty-year-in-residence dust effect, that inhaled 10 years before, a 10-year effect, and so on. Yesterday's dust, although perhaps most readily at hand, best measured and analyzed, is likely also the least related to the disease findings in the individual.

Appreciation of this sequence of events leads to a number of conclusions. First, in many instances, disease now being seen is the result of work conditions in the 1920's, 1930's, and 1940's. Since few environmental measurements were made in those years, there is considerable difficulty now in determining dose–disease response relationships for the setting of exposure

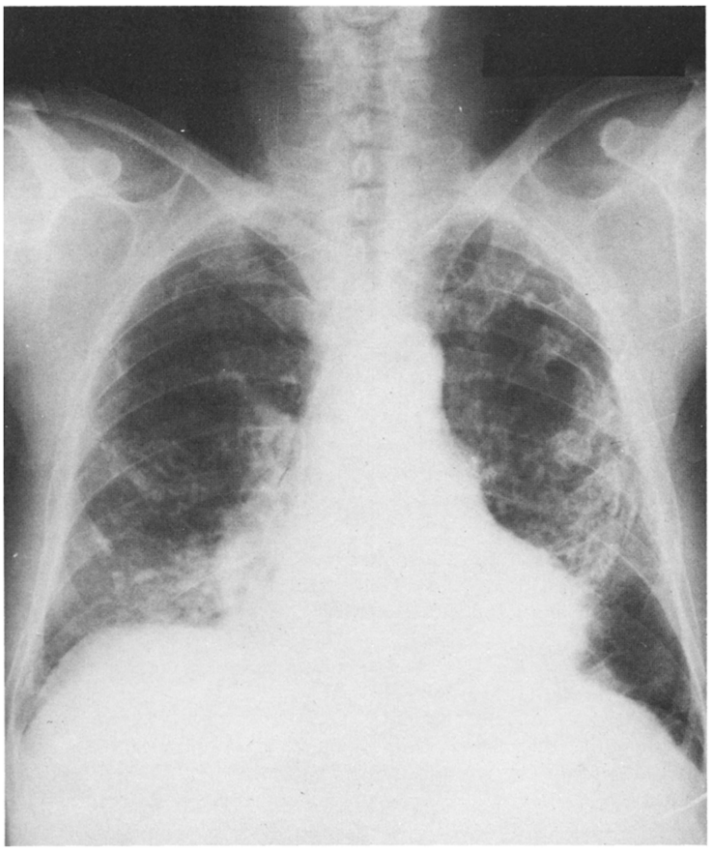

FIG. 12. June 25, 1971. Continued progression has resulted in pulmonary insufficiency and retirement because of disability. This sequence of films demonstrates the importance of progression without further exposure, decades after brief initial occupational exposure.

standards for the workplace; one-half of the equation is uncertain. By the same token, exposures today will be reflected in disease in the year 2,000, stressing the importance of preventive measures at present. Although we can now undertake environmental evaluation, evaluation of their effectiveness is hampered by the absence of the other half of the equation.

Second, from a practical point of view, seeking a possible occupational cause for lung disease is facilitated by investigating work exposures for the entire lifetime of the individual. What he did at age 16 may be much more important than his work at 60. A full, detailed occupational history (not merely job classifications) can be far more rewarding than tomograms or closing volumes or serum protein fractionation (Figs. 9–12).

Brief exposure followed by a long period of lung residence may be particularly important in occupational lung cancer and pleural mesothelioma, since often much less exposure is required to induce neoplasms than pulmonary fibrosis. As a result, many instances of such neoplasms are seen without

roentgenological evidence of pneumoconiosis, and the relation of the neoplasm to prior occupational exposure may remain obscure unless work exposures decades before are considered.

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REFERENCES

1. AGRICOLA, G. "De Re Metallica." (1556) Translated by Herbert C. Hoover and Lou H. Hoover. Dover Publications, New York, 1950.
2. ALLISON, A. C. Lysosomes and the toxicity of particulate pollutants. *Arch. Int. Med.* **128**, 131–139 (1971).
3. ARCHER, V. E. AND LUNDIN, F. E. Radiogenic lung cancer in man: exposure–effect relationship. *Environ. Res.* **1**, 370–383 (1967).
4. AUERBACH, O., STOUT, A. P., HAMMOND, E. C., AND GARFINKEL, L. Smoking habits and age in relation to pulmonary changes: rupture of alveolar septums, fibrosis and thickening of walls of small arteries and arterioles. *N. Engl. J. Med.* **269**, 1045–1054 (1963).
5. AVILA, R. AND VILLAR, T. G. Suberosis respiratory disease in cork workers. *Lancet* **1**, 620–621 (1968).
6. BAILEY, W. C., BROWN, W., BUECHNER, H. A., WEILL, H., AND ZISKIND, M. Silico-mycobacterial disease in sandblasters. *in* "Trans. 31st V.A.–Armed Forces Pulmonary Disease Research Conference, p. 4. Veterans Administration, Washington, D. C., 1972.
7. BARRIE, H. J. AND GOSSELIN, L. Massive pneumoconiosis from a rock dust containing no free silica. Nepheline lung. *Arch. Environ. Health* **1**, 109–117 (1960).
8. BATAWI, M. A. EL, AND HUSSEIN, M. Endemic byssinosis in an Egyptian village. *Brit. J. Ind. Med.* **2**, 231–234 (1964).
9. BERSON, S. A., YALOW, R. S., SAITO, T., AND SELIKOFF, I. J. Antibodies to "Alcalase" after industrial exposure. *N. Engl. J. Med.* **284**, 688–690 (1971).
10. BEIRNE, G. J. AND BRENNAN, J. T. Glomerulonephritis associated with hydrocarbon solvents, mediated by antiglomerular basement membrane antibody. *Arch. Environ. Health* **25**, 365–369 (1972).
11. BOHLIG, H. Radiological classification of pulmonary asbestosis. *Ann. N. Y. Acad. Sci.* **132**, 338–350 (1965).
12. BOREN, H. G. Pathobiology of air pollutants. *Environ. Res.* **1**, 178–197 (1967).
13. BOUHUYS, A. *et al.* Byssinosis in the United States. *N. Engl. J. Med.* **277**, 170 (1967).
14. BOYD, J. T., DOLL, R., FAULDS, J. S., AND LEIPER, J. The report of the MRC statistical unit on the incidence of lung cancer in hematite mines. *Brit. J. Ind. Med.* **27**, 97 (1970).
15. BUECHNER, H. A. AND ANSARI, A. Acute silico-proteinosis. *Dis. Chest* **55**, 274 (1969).
16. BURRELL, R. Immunological aspects of coal workers' pneumoconiosis. *Ann. N. Y. Acad. Sci.* **200**, 94–105 (1972).
17. CAPLAN, A., PAYNE, R. B., AND WHITNEY, J. L. A broader concept of Caplan's syndrome related to rheumatic factors. *Thorax* **17**, 205–212 (1962).
18. CHESNER, C. Pulmonary granulomatosis in residents of community near beryllium plant: three autopsied cases. *Ann. Int. Med.* **32**, 1028 (1950).

19. COATES, E., JR. AND WATSON, J. H. L. Diffuse interstitial disease in tungsten carbide workers. *Ann. Int. Med.* **75**, 709–716 (1971).
20. COETZEE, A. M. Chronic bronchitis in the gold mining industry. *Proc. Mine Med. Affairs Assoc., Congr. Rec.* **71**, 84–93 (1971).
21. COFFIN, D. L. AND BLOOMER, E. J. Acute toxicity of irradiated auto exhaust and its indication of enhancement of mortality from streptococcal pneumonia. *Arch. Environ. Health* **15**, 36 (1967).
22. COLLIS, E. L. Milroy Lecture. Industrial pneumoconiosis, with special reference to dust-phthisis. *Public Health (London)* **28**, 252–292; **29**, 11–37 (1915).
23. COLLIS, E. L. AND GILCHRIST, J. C. Effects of dust upon coal trimmers. *J. Ind. Hyg.* **10**, 101 (1928).
24. CONNEY, A. H. AND BURNS, J. J. Metabolic interactions among environmental chemicals and drugs. *Science* **178**, 576–586 (1972).
25. COOKE, W. E. Pulmonary asbestosis. *Brit. Med. J.* **2**, 1024–1025 (1927).
26. DAVIDSON, J. K. AND MACPHERSON, P. Pulmonary changes in paraquat poisoning. *Clin. Radiol.* **23**, 18–25 (1972).
27. DESSAUER, P., BAIER, E. J., CRAWFORD, G. M. AND BEATTY, J. A. Development of patterns of coal workers' pneumoconiosis in Pennsylvania and its association with respiratory impairment. *Ann. N. Y. Acad. Sci.* **200**, 220–251 (1972).
28. DE VILLIERS, A. J. AND WINDISH, J. P. Lung cancer in a fluorspar mining community. I. Radiation, dust, and mortality experience. *Brit. J. Ind. Med.* **21**, 94–109 (1964).
29. DICKIE, H. A. AND RANKIN, J. Farmer's lung. An acute granulomatous interstitial pneumonitis occurring in agricultural workers. *J. Amer. Med. Ass.* **167**, 1069 (1958).
30. DOLL, R. Mortality from lung cancer in asbestos workers. *Brit. J. Ind. Med.* **12**, 81–86 (1955).
31. EDENFIELD, R. W. A clinical and roentgenological study of kaolin workers. *Arch. Environ. Health* **1**, 392–403 (1960).
32. Editorial. Goodpasture's syndrome and exposure to solvents. *J. Amer. Med. Ass.* **222**, 1555 (1972).
33. EISENBUD, M., WANTA, R. C., SUNSTAN, C., STEADMAN, L. T., HARRIS, W. B. AND WOLF, B. S. Non-occupational berylliosis. *J. Ind. Hyg.* **31**, 282–294 (1949).
34. ENTERLINE, P. E. A review of mortality data for American coal miners. *Ann. N. Y. Acad. Sci.* **200**, 260–272 (1972).
35. ENTICKNAP, J. B. AND SMITHER, W. J. Peritoneal tumours in asbestosis. *Brit. J. Ind. Med.* **21**, 20–31 (1964).
36. ERIKSSON, S. Studies in alpha 1-antitrypsin deficiency. *Acta Med. Scand. Suppl.* **177** (1967).
37. FAULDS, J. S. AND STEWART, M. J. Carcinoma of the lung in haematite miners. *J. Pathol. Bacteriol.* **72**, 353–366 (1956).
38. FLINDT, M. L. H. Pulmonary disease due to inhalation of derivatives of Bacillus subtilis containing proteolytic enzyme. *Lancet* **1**, 1177–1181 (1969).
39. GILSON, J. C. Occupational Bronchitis (?). *Proc. Roy. Soc. Med.* **63**, 857–864 (1970).
40. GLOYNE, S. R. The morbid anatomy and histology of asbestosis. *Tubercle* **14**, 550–558 (1933).
41. GORALEWSKI, G. Zur klinik der aluminiumlunge. *Arch. Gewerbepath.* **11**, 106–113 (1941).
42. GOUGH, J., RIVERS, D., AND SEAL, R. M. E. Pathological studies of modified pneumoconiosis in coal miners with rheumatoid arthritis (Caplan's syndrome.) *Thorax* **10**, 9–18 (1955).
43. GRANT, I. W. B. *et al.* Prevalence of farmer's lung in Scotland: a pilot survey. *Brit. Med. J.* **1**, 530–534 (1972).
44. GRENFELL, D. AND GILMOUR, J. Cancer among nickel workers. *Lancet* **2**, 1086–1087 (1932).
45. HADDOW, A. C. Report of Annual Meeting of British Medical Association, Manchester, 1929. *Lancet* **2**, 230 (1929).
46. HAMMOND, E. C. AND SELIKOFF, I. J. The effects of air pollution; epidemiological evidence, *in* "Pneumoconiosis. Proceedings Int. Conf. Johannesburg, 1969" (H. A. Shapiro, Ed.), pp. 368–373. Oxford Univ. Press, Capetown, 1970.
47. HARDY, H. L. Delayed chemical pneumonitis occurring in workers exposed to beryllium compound. *J. Ind. Hyg.* **28**, 197 (1946).

48. HARINGTON, J. S. Investigative techniques in the laboratory study of coal workers pneumoconiosis: recent advances at the cellular level. *Ann. N. Y. Acad. Sci.* **200**, 816–834 (1972).
49. HARINGTON, J. S., MILLER, K., AND MACNAB, G. Hemolysis by asbestos. *Environ. Res.* **4**, 95–117 (1971).
50. HARRIS, R. L., JR. A model for deposition of microscopic fibers in the human respiratory system. Thesis, Univ. of North Carolina, 1972.
51. HARTING, F. H. AND HESSE, W. Der lungenkrebs, die bergenkrakheit in den Schneeberger gruben. Vierteljahr *esschr. Gerichtl. Med. Oeff. Sanit.* **30**, 296; **31**, 102 and 313 (1879).
52. HEIMANN, H. *et al.* Silicosis in mica mining in Bihar, India. *Arch. Ind. Hyg. Occup. Med.* **8**, 420–435 (1953).
53. HEPPLESTON, A. G. The pathological recognition and pathogenesis of emphysema and fibrocystic disease of the lung with special reference to coal workers. *Ann. N. Y. Acad. Sci.* **200**, 347–369 (1972).
54. HIGGINS, I. T. T. Chronic respiratory disease in mining communities. *Ann. N. Y. Acad. Sci.* **200**, 197–210 (1972).
55. HIGGINS, I. T. T., OLDHAM, P. D., COCHRANE, A. L., AND GILSON, J. C. Respiratory symptoms and pulmonary disability in an industrial town. *Brit. Med. J.* **2**, 904–910 (1956).
56. HOLADAY, D. A. History of the exposure of miners to radon. *Health Phys.* **16**, 547–552 (1969).
57. International Labour Office/UC. "International classification of radiographs of pneumoconiosis, 1971, "Occupational Safety and Health Series 22 (Rev.), International Labour Office, Geneva, 1972.
58. KALACIĆ, I. Chronic nonspecific lung disease in cement workers. *Arch. Environ. Health* **26**, 78–83 (1973).
59. KAW, J. L. AND ZAIDI, S. H. Pathogenesis of pulmonary silicosis in rats fed stock and multideficient diet since weaning. *Environ. Res.* **3**, 199–211 (1970).
60. KIVILUOTO, R. Pleural calcification as a roentgenologic sign of non-occupational endemic anthopyllite-asbestosis. *Acta Radiol. Suppl.* **194**, 1–67 (1960).
61. KLEINFELD, M. *et al.* Mortality among talc miners. *Arch. Environ. Health* **14**, 663 (1967).
62. KLEMPERER, P. AND RABIN, C. B. Primary neoplasms of the pleura. A report of five cases. *Arch. Pathol.* **11**, 385–412 (1931).
63. KOSHURNIKOVA, N. A. *et al.* Mechanism of development of plutonium induced pulmonary sclerosis. *Health Phys.* **22**, 753–754 (1972).
64. KOVEN, A. L. *et al.* "Health of workers in the chromate producing industry. A study. "PHS Publication No. 192, U. S. Govt. Printing Office, 1953.
65. LANGER, A. M. *et al.* Identification of asbestos in human tissues. *J. Occup. Med.*, **15**, 287–295 (1973).
66. LANGER, A. M. AND MACKLER, A. D. Mineral particles and human disease, *in* "Encyclopedia of Geochemistry and Environmental Sciences" (R. W. Fairbridge, (Ed.), Vol. 4A, pp. 730–739. Van Nostrand-Reinhold, New York, 1972.
67. LANGER, A. M., RUBIN, I. B., AND SELIKOFF, I. J. Chemical characterization of asbestos-body cores by electron microprobe analysis: *Histochem. Cytochem.* **20**, 723–734 (1972).
68. LANGER, A. M., RUBIN, I. B., SELIKOFF, I. J., AND POOLEY, F. D. Chemical characterization of uncoated asbestos fibers from the lungs of asbestos workers by electron microprobe analysis. *Histochem. Cytochem.* **20**, 735–740 (1972).
69. LANGER, A. M., SELIKOFF, I. J., AND SASTRE, A. Chrysotile asbestos in the lungs of persons in New York City. *Arch. Environ. Health* **22**, 348–361 (1971).
70. LASKIN, S., KUSCHNER, M., DREW, R. T., CAPPIELLO, V. P., AND NELSON, N. Tumors of the respiratory tract induced by inhalation of Bis(chloromethyl)ether. *Arch. Environ. Health* **23**, 135–136 (1971).
71. LEE, D. H. K. AND KOTIN, P. "Multiple factors in the causation of environmentally induced disease," pp. 225. Academic Press, New York, 1972.
72. LIPPMAN, M. AND GOLDSTEIN, D. Oil-mist studies, environmental evaluation and control. *Arch. Environ. Health* **21**, 591–599 (1970).

73. LLOYD, J. W. Long term mortality study of steel workers. V. Respiratory cancer in coke plant workers. *J. Occupat. Med.* **13,** 53–68 (1971).
74. LOWE, C. R. Industrial bronchitis. *Brit. Med. J.* **1,** 463–486 (1969).
75. LUNDIN, F. E., JR., LLOYD, J. W., SMITH, E. M., ARCHER, V. E., AND HOLADAY, D. A. Mortality of uranium miners in relation to radiation exposure, hard-rock mining and cigarette smoking 1950 through Sept. 1967. *Health Phys.* **16,** 571–578 (1969).
76. LUPU, N. AND VELIKAN, K. Pneumoconiosis in children of industrial cities, with SiO_2 air pollution. *Gig. Sanit.*, 10–13, 1958.
77. MÄÄTTÄ, K., ELO, R., ARSTILA, A., AND UKSILA, E. Pulmonary changes induced by titanium dioxide. *Duodecim* **87,** 1435–1444 (1971).
78. MACKLEM, P. T. Obstruction in small airways—a challenge to medicine. *Amer. J. Med.* **52,** 721–724 (1972).
79. MANCUSO, T. F. Relation of duration of employment and prior respiratory illness to respiratory cancer among beryllium workers. *Environ. Res.* **3,** 251 (1970).
80. MATOLO, N. M., KLAUBER, M. R., GORISHEK, W. M., AND DIXON, J. A. High incidence of gastric carcinoma in a coal mining region. *Cancer* **29,** 733–737 (1972).
81. MCCALLUM, R. I. Decompression sickness. *Brit. J. Ind. Med.* **25,** 4 (1968).
82. MCCOMBS, R. A. Disease due to immunologic reactions in the lungs. *N. Engl. J. Med.* **286,** 1245–1252 (1972).
83. MCLAUGHLIN, A. I. G. "Industrial lung disease of iron and steel foundry workers." Her Majesty's Stationery Office, London, 1950.
84. MEIKLEJOHN, A. History of lung diseases of coal miners in Great Britain: Part I. 1800–1875. Brit. J. Ind. Med. **8,** 127 (1951); Part II. 1875–1920. *Brit. J. Ind. Med.* **9,** 93 (1951); Part III. 1920–1952. *Brit. J. Ind. Med.* **9,** 208 (1952).
85. MERCHANT, J. A., KILBURN, K. H., O'FALLON, W. M., HAMILTON, J. D., AND LUMSDEN, J. C. Byssinosis and chronic bronchitis among cotton textile workers. *Ann. Int. Med.* **76,** 423–433 (1972).
86. MEREWETHER, E. R. A. AND PRICE, C. V. Report on effects of asbestos dust on the lungs and dust suppression in the asbestos industry. Part I. Occurrence of pulmonary fibrosis and other pulmonary affections in asbestos workers." Her Majesty's Stationary Office, London, England, 1930.
87. MILLER, A., TEIRSTEIN, A., BADER, M. E., BADER, R. A., AND SELIKOFF, I. J. Talc pneumoconiosis: significance of sublight microscopic particles. *Amer. J. Med.* **50,** 395–402 (1971).
88. MILLER, L., SMITH, W. E., AND BERLINER, S. W. Tests for effect of asbestos on benzo[*a*]pyrene carcinogenesis in the respiratory tract. *Ann. N. Y. Acad. Sci.* **132,** 489–500 (1965).
89. MOSS, E., SCOTT, T. S., AND ATHERLEY, G. R. G. Mortality of newspaper workers from lung cancer and bronchitis 1952–1966. *Brit. J. Ind. Med.* **29,** 1–14 (1972).
90. MYERS, C. E. Anthracosilicosis and bronchogenic carcinoma. *Dis. Chest* **52,** 800–805 (1967).
91. NAEYE, R. L. Types of fibrosis in coal workers' pneumoconiosis. *Ann. N. Y. Acad. Sci.* **200,** 381–400 (1972).
92. NAGELSCHMIDT, G. The relation between lung dust and lung pathology in pneumoconiosis. *Brit. J. Ind. Med.* **17,** 247 (1960).
93. NEWHOUSE, M. L. AND THOMPSON, H. Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. *Brit. J. Ind. Med.* **22,** 261–269 (1965).
94. PASTERNACK, B. AND EHRLICH, L. Occupational exposure to an oil mist atmosphere. *Arch. Environ. Health* **25,** 286–294 (1972).
95. PENDERGRASS, E. P. *et al.* Roentgenological patterns in lung changes that simulate those found in coal workers' pneumoconiosis. *Ann. N. Y. Acad. Sci.* **200,** 494–502 (1972).
96. PENDERGRASS, E. P. *et al.* Observations on workers in the graphite industry. Part 1. *Med. Radiogr. Photogr.* **43,** 70–99 (1967); Part 2. *Med. Radiogr. Photogr.* **44,** 2–17 (1968).
97. PEPYS, J. "Hypersensitivity Diseases of the Lungs Due to Fungi and Organic Dusts. Monographs in Allergy," Vol. 4. Karger, Basel, Switzerland, 1969.
98. PERNIS, B., VIGLIANI, E. C., AND SELIKOFF, I. J. Rheumatoid factor in serum of individuals exposed to asbestos. *Ann. N. Y. Acad. Sci.* **132,** 112–120 (1965).

99. PHIBBS, B. P., SUNDIN, R. E., AND MITCHELL, R. S. Silicosis in Wyoming bentonite workers. *Amer. Rev. Resp. Dis.* **103,** 1–17 (1971).
100. PIMENTEL, J. Furrier's Lung. *Thorax* **25,** 387–398 (1970).
101. PIRCHAN, A. AND SIK, H. Cancer of the lung in the miners of Jachymov (Joachimstal). Report of cases observed in 1929–1930. *Amer. J. Cancer* **16,** 681–722 (1932).
102. RATNOFF, O. D. The interrelationships of clotting and immunologic mechanisms. *Hosp. Pract.*, 119–132 (1971).
103. ROBERTSON, A. J. The romance of tin. *Lancet,* **1** 1229–1236 and 1289–1293 (1964).
104. "Report of task force on research in respiratory diseases." Lung Program, National Heart and Lung Institute, U. S. Dept. HEW, Bethesda, MD. 1972, p. 243.
105. ROSS, M. H. The Appalachian coal miner: his way of living, working and relating to others. *Ann. N. Y. Acad. Sci.* **200,** 184–196 (1972).
106. ROSSITER, C. E. Relation of lung dust content to radiological changes in coal workers. *Ann. N. Y. Acad. Sci.* **200,** 465–477 (1972).
107. RYDER, R. C., LYONS, J. P., CAMPBELL, H., AND GOUGH, J. Bronchial mucous gland status in coal workers' pneumoconiosis, *Ann. N. Y. Acad. Sci.* **200,** 370–380 (1972).
108. SADOUL, P., SENAULT, R., MACINOT, C., AUBERTIN, N., AND GUILLERM, J. La pneumoconiose des mineurs de fer du Bassin de Lorraine. *La Rev. Pract.* **8,** 1505–1509 (1958).
109. SAFFIOTTI, U. Experimental respiratory tract carcinogenesis. *Progr. Exp. Tumor Res.* **11,** 302–333 (1967).
110. SCHLIPKÖTER, H. W. Possibilities of causal prophylaxis and therapy of pneumoconiosis. *Arch. Environ. Health* **21,** 181–191 (1970).
111. SCHNITZER, R. J., BUNESCU, G., AND BADEN, V. Interaction of mineral fiber surfaces with cells *in vitro*. *Ann. N. Y. Acad. Sci.* 172:759–772, 1971.
112. SCHNITZER, R. J., AND PUNDSACK, F. L. Asbestos hemolysis. *Environ. Res.* **3,** 1–13 (1970).
113. SEAL, R. M. E., HAPKE, E. J., AND THOMAS, G. O. The pathology of the acute and chronic stages of farmer's lung. *Thorax* **23,** 469 (1968).
114. Section of Occupational Medicine, Roy. Soc. Med. Symposium on Isocyanates. *Proc. Roy. Med.* **63,** 365 (1969).
115. SELIKOFF, I. J. The occurrence of pleural calcification among asbestos insulation workers. *Ann. N. Y. Acad. Sci.* **132,** 351–367 (1965).
116. SELIKOFF, I. J. Occupational lung disease, *in* "Environmental Factors in Respiratory Disease" (Douglas H. K. Lee, Ed.), pp. 199–217. Academic Press, New York, 1972.
117. SELIKOFF, I. J., CHURG, J., AND HAMMOND, E. C. Asbestos exposure and neoplasia. *J. Amer. Med. Ass.* **188,** 22–26 (1964).
118. SELIKOFF, I. J., CHURG, J., AND HAMMOND, E. C. The occurrence of asbestosis among insulation workers in the United States. *Ann. N. Y. Acad. Sci.* **132,** 139–155 (1965).
119. SELIKOFF, I. J., CHUNG, J., AND HAMMOND, E. C. Relation between exposure to asbestos and mesothelioma. *N. Engl. J. Med.* **272,** 560–565 (1965).
120. SELIKOFF, I. J. AND HAMMOND, E. C. Community effects of non-occupational environmental asbestos exposure. *Amer. J. Pub. Health* **58,** 1658–1666 (1968).
121. SELIKOFF, I. J., HAMMOND, E. C., AND CHURG, J. Asbestos exposure, smoking and neoplasia. *J. Amer. Med. Ass.* **204,** 106–112 (1968).
122. SELIKOFF, I. J., HAMMOND, E. C., AND SEIDMAN, H. Cancer risk of insulation workers in the United States, *in* "Working Group to Assess Biological Effects of Asbestos," Int. Agency for Res. on Cancer, Lyon, October 1972. (in press).
123. SHAVER, C. G. AND RIDDEL, A. R. Lung changes associated with manufacture of alumina abrasives. *J. Ind. Hyg. Toxicol.* **29,** 145 (1947).
124. SIEGAL, W., SMITH, A. R., AND GREENBURG, L. Study of talc miners and millers in St. Lawrence County, New York, *Ind. Bull.* **22,** 468–469 (1943).
125. SLUIS-CREMER, G. K., WALTERS, L. G., AND SICHEL, H. S. Chronic bronchitis in miners and non-miners: an epidemiological survey of a community in the gold mining area in the Transvaal. *Brit. J. Ind. Med.* **24,** 1–12 (1967).
126. SMITH, A. R. Pleural calcification resulting from exposure to certain dusts. *Amer. J. Roentol.* **67,** 375–382 (1952).

127. SMITH, K. W. Trends in the health of the asbestos worker. *Ann. N. Y. Acad. Sci.* **132**, 685–690 (1965).
128. SMYTH, L. T., RUHF, R. C., WHITMAN, N. E., AND DUGAN, T. Clinical manganism and exposure to manganese in the production and processing of ferromanganese alloy. *J. Occup. Med.* **15**, 101–109 (1973).
129. South African Medical Research Council. "Annual report 1971 of the National Research Institute for Occupational Diseases." p. 44. Johannesburg, 1972.
130. "Standard for exposure to asbestos dust." *Federal Register* **37**, No. 110, 1972.
131. STANTON, M. AND WRENCH, C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J. Nat. Cancer Inst.* **48**, 791–821 (1972).
132. STEWART, M. J. AND FAULDS, J. S. The pulmonary fibrosis of hematite miners. *J. Pathol. Bacteriol.* **39**, 233–253 (1934).
133. SUNDERMAN, F. W., JR. The current status of nickel carcinogenesis. *Ann. Clin. Lab. Sci.* (in press) (1973).
134. SZCZEKLIK, A., STANKOWSKA, K., AND FRYDECKA, I. Cardiopulmonary function in α_1-antitrypsin heterozygotes exposed to severe air pollution. *Amer. Rev. Resp. Dis.* **107**, 289–291 (1973).
135. TURKEVICH, J. The world of fine particles. *Amer. Sci.* **47**, 97–119 (1959).
136. TURNER-WARWICK, M. AND PARKES, W. R. Circulating rheumatoid and antinuclear factors in asbestos workers. *Brit. Med. J.* **2**, 492–495 (1970).
137. VIGLIANI, E. C. AND PERNIS, B. An immunological approach to silicosis, *in* "Proc. Pneumocon. Conf. Johannesburg." (A. J. Orenstein, Ed.), pp. 395–407. Churchill, London, 1959.
138. VOLKHEIMER, G., SCHULZ, F. H., LINDENAU, A., AND BEITZ, U. Persorption of metallic iron particles. *Gut* **10**, 32–33 (1969).
139. WAGNER, J. C., SLEGGS, C. A., AND MARCHAND, P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Brit. J. Ind. Med.* **17**, 260–271 (1960).
140. WAGONER, J. K., MILLER, R. W., LUNDIN, F. E., JR., FRAUMENI, J. J. F., JR., AND HAIJ, M. E. Unusual cancer mortality among a group of underground metal miners. *N. Engl. J. Med.* **269**, 284–289 (1963).
141. WALKER, D. D., ARCHIBALD, R. M., AND ATTFIELD, M. D. Bronchitis in men employed in the coke industry. *Brit. J. Indust. Med.* **28**, 358–363 (1971).
142. WEISS, W. Cigarette smoking, asbestosis and pulmonary fibrosis. *Amer. Rev. Resp. Dis.* **104**, 223–227 (1971).
143. WELLER, W. AND ULMER, W. T. Treatment of pneumoconiosis caused by coal-quartz dusts with polyvinyl-pyridine-*N*-oxide (P204). *Ann. N. Y. Acad. Sci.* **200**, 624–632 (1972).
144. ZENKER, F. A. Ueber staubinhalationskrankheiten der lungen. *Deutsche Arch. Klin. Med.* **2**, 116 (1867).