OCCUPATIONAL RESPIRATORY DISEASES

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

Associate Editors
Brian A. Boehlecke, M.D.
Geoffrey Taylor, M.D.

Technical Editor
Molly Pickett-Harner, M.F.A.

Division of Respiratory Disease Studies
Appalachian Laboratory for Occupational Safety and Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

September 1986

Disclaimer

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

DHHS (NIOSH) Publication No. 86-102

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

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 FEV_1 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)

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, cotton 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 FEV_1 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 SO_2 and respirable dust, they could find no convincing effect that SO_2 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 FEV_1 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 FEV_1's were at the lower end of predicted in 27 workers at a cadmium battery plant in Birmingham, England (1). Kazantsis 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 noncoal 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. Naeye 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 affect 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 bronchitis (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—alpha$_1$-antitrypsin and alpha$_2$-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 circumference 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 bronchopulmonary 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 nonspecific. 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 ⅔ 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 alpha$_1$-anti-trypsin in emphysema. Only approximately 1:2,000 of the U.S. population are homozygous for alpha$_1$-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 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.

*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.

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 B_2 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-sulfamethoazole 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). Crofton 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 1/y and a fall in FVC of 0.64 1/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 proceeded 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 $FEV_{1\text{-}0}$ 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. Brit J Ind Med *19*:65-76, 1962.
0.024 Nonsmokers	Higgins, I.T.T.: Tobacco smoking, respiratory symptoms and ventilatory capacity. Brit Med J *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. Am J Med *30*:243-258, 1961.
3. 0.024	Ferris, B.G., Anderson, P.O., and Zinkmantel, R.: Prediction values for screening tests of pulmonary function. Am Rev Respir Dis *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. Am Rev Respir Dis *94*:74-77, 1966.
5. 0.026 (904) Smoking	Fletcher, C.M.: Bronchial infections and reactivity in chronic bronchitis. J. Roy. Coll. Physicians, London *2*:183-190, 1968.
Age 6. 0.032 25-34 0.041 55-64 (756)	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. Am J Pub Health *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. Brit Med J *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. Brit J Ind Med *27*:326-333, 1967.
Age 9. 0.43 25-34 0.027 35-44 0.029 45-54 0.053 55-64	Morris, J.F., Kowski, A., and Johnson, L.C.: Spirometer standards for healthy nonsmoking adults. Am Rev Respir Dis *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. Included 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 mainline 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/m^3 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 occurrring together.

A problem which can be surmounted by clear definitions is differentiation of the syndrome 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 phosgene (in the chemical industry) or to SO_2 (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.

REFERENCES

1. Adams, R.G., Harrison, J.F., and Scott, P.: The development of cadmium-induced proteinuria, impaired renal function, and osteomalacia in alkaline battery workers. Q J Med NS *38:*425-443, 1969.
2. Albert, R. E. and Arnette, L.C.: Clearance of radioactive dust from the human lung. Arch Ind Hlth *12:*99-106, 1955.
3. Amandus, H.E., Lapp, N.L., Jacobson, G., and Reger, R.B.: Significance of irregular small opacities in radiographs of coal-miners in ths USA. Br J Ind Med *33:*13-17, 1976.
4. Asmundsson, T. and Kilburn, K.H.: Survival of acute respiratory failure: a study of 239 episodes. Ann Intern Med *70:* 471-485, 1969.
5. Asmundsson, T. and Kilburn, K. H.: Survival of acute respiratory failure: long-term survival. Ann Intern Med *80:*54-57, 1974.
6. Auerbach, O., Stout, A. P., Hammond, E. C., and Garfinkel, L.: Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. N Engl J Med *265:*253-267, 1961.
7. Bates, D. V.: The fate of the chronic bronchitic: a report of the ten-year follow-up in the Canadian Department of Veteran's Affairs Coordinated Study of Chronic Bronchitis. Am Rev Respir Dis *108:*1043-1065, 1973.
8. Becklake, M. R., Goldman, H. I., Bosman, A. R., and Freed, C. C.: The Long-term effects of exposure to nitrous fumes. Am Rev Tuberc *76:*398-409, 1957.
9. Berry, G., Molyneux, M. K. B., and Tombleson, J. B. L.: Relationship between dust level and byssinosis and bronchitis in Lancashire cotton mills. Br J Ind Med *31:*18-27,1974.
10. Bignon, J., Khory, F., Evan, P., Andre, J. and Brouet, G.: Morphometric study in chronic obstructive bronchopulmonary disease. Am Rev Respir Dis *99:*669-695, 1969.
11. Bonnell, J. A.: Emphysema and proteinuria in men casting copper-cadmium alloys. Br J Ind Med *12:*181-195, 1955.
12. Boushy, S. F., Adhikari, P. K., Sakamoto, A., and Lewis, B. M.: Factors affecting prognosis in emphysema. Dis Chest *45:*402-411, 1964.
13. Brinkman, G. L. and Block, D. L.: The prognosis in chronic bronchitis. JAMA *197:*71-77, 1966.
14. Burrows, B. and Earle, R. H.: Course and prognosis of chronic obstructive lung disease, a prospective study of 200 patients. N Engl J Med *280:*397-404, 1969.
15. Camner, P., Helstroem, P. A., and Philip-

son, K.: Carbon dust and mucociliary transport. Arch Environ Health *26:*294-296, 1973.
16. Chan-Yeung, M., Ashley, M. J., Corey, P., Wilson, G., Dorken, E., and Grzybowski, S.: A respiratory survey of cedar mill workers. JOM *20:*323-327, 1978.
17. Chan-Yeung, M., Barton, L. M., and Grzybowski, S.: Occupational asthma and rhinitis due to Western red cedar (Thuja plicata). Am Rev Respir Dis *108:*1094-1102, 1973.
18. Chodosh, S. and Medici, T.C.: The bronchial epithelium in chronic bronchitis. I. Exfoliative cytology during stable, acute bacterial infection and recovery phases. Am Rev Respir Dis *104:*888-898, 1971.
19. Chodosh, S., Zacceo, C. W., and Segal, M. S.: The cytology and histochemistry of sputum cells. Am Rev Respir Dis *85:*635-648, 1962.
20. Ciba Guest Symposium. Terminology, definitions and classification of chronic pulmonary emphysema and related condition. Thorax *14:*286-299, 1959.
21. Coates, E. O. Jr. and Watson, J. H. L.: Diffuse interstitial lung disease in tungsten carbide workers. Ann Intern Med *75:*709-716, 1971.
22. Cosio, M., Ghezzo, H., Hogg, J. C., Corbin, R., Loveland, M., Dosman, J., and Macklem, P. T.: The relationships between structural changes in small airways and pulmonary-function tests. N Engl J Med *298:*1277-1281, 1978.
23. Croften, E. C.: A study of lung cancer and bronchitis mortality in relation to coalmining in Scotland. Br J Prev Soc Med *23:*141-144, 1969.
24. Davies, T. A. L.: Respiratory disease in founrymen. London: H. M. S. O., 1971.
25. Deutsche Forschungsgemeinschaft. Research report. Chronic bronchitis and occupational dust exposure: cross sectional study of occupational medicine on the significance of chronic inhalative burdens for the broncho-pulmonary system. Boppard: Harald Bolat Verlag K. G., 1978.
26. Ebert, R. V. and Terracio, M. J.: The bronchiolar epithelium in cigarette smokers. Observations with the scanning electron microscope. Am Rev Respir Dis *111:*4-11, 1975
27. Edwards, C., Macartney, J., Rooke, G., and Ward, F.: The pathology of the lung in byssinosis. Thorax *30:*612-623, 1975.
28. Enterline, P.E.: the effects of occupation on chronic respiratory disease. Arch Environ Health *14:*189-200, 1967.
29. Eriksson, S.: Studies in alpha$_1$-antitryspin deficiency. Acta Meda Scand *177:*1-85, 1965.
30. Fletcher, C. M.: Disability and mortality from chronic bronchitis in relation to dust exposure. Arch Ind Health *18:*368-373, 1958.
31. Fletcher, C. M. and Petro, R.: A natural history of chronic airflow obstuction. Br Med J *1:*1645-1648, 1977.
32. Fletcher, C. M., Petro, R., Rinker, C., and Speizer, F. E.: the Natural History of Chronic Bronchitis and Emphysema (an eight year study of early chronic obstructive lung disease in working men in London). Oxford: Oxford University Press, 1976.
33. Friberg, L.: Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. Acta Med Scan *138:*7-124, 1950.
34. Gandevia, B.: Clinical history, physical examination and x-ray change, in Pulmonary Reactions to Organic Materials, Kilburn, K. H. (ed.). Ann NY Acad Sci *221:*10-26, 1974.
35. Gandevia, B. and Ritchie, B.: Relevance of respiratory systems and signs to ventilatory capacity changes after exposure to grain dust and phosphate rock dust. Br J Ind Med *23:*181-187, 1966.
36. Gilson, J. C.: Occupational bronchitis? Proc R Soc Med *63:*857-864, 1970.
37. Glynn, A. A.: Pathology of chronic bronchitis. Br Med J *1:*127-128, 1961.
38. Goodman, N., Lane, R. E., and Rampling, S. B.: Chronic bronchitis: an introductory examination of existing data. Br Med J *2:*237-243, 1953.
39. Gough, J.: Discussion on the diagnosis of pulmonary emphysema. Proc R Soc Med *45:*576-577, 1952.
40. Gough, J.: The pathogenesis of emphysema, in the lung, A. A. Liebow and D. C. Smith (eds). Baltimore: Williams and Wilkins Co. 109-133, 1968.

41. Gough, J.: Pneumoconiosis in coal trimmers. J Pathol Bate *51:*277-285, 1940.
42. Gregory, J.: A study of 340 cases of chronic bronchitis. Arch Environ Health *22:* 428-439, 1971.
43. Gross, P., Babyak, M. A., Tolker, E., and Kaschak, M.: Enzymatically produced pulmonary emphysema. JOM *6:*481-484, 1964.
44. Harris, T. R., Pratt, P. C., and Kilburn, K.H.: Total lung capacity measured by roentgenograms. Am J Med *50:*756-764, 1971.
45. Heppleston, A. G.: The essential lesion of pneumoconiosis in Welsh coal workers. J Pathol Bact *59:*453-460, 1947.
46. Heppleston, A. G. and Leopold, J. G.: Chronic pulmonary emphysema. Am J Med *31:*279-291, 1961.
47. Higgins, I. T. T. and Cochrane, A. L.: Chronic respiratory disease in a random sample of men and women in the Rhondda Fach in 1958. Br J Ind Med *18:*93-102, 1961.
48. Higgins, I. T. T., Cochrane, A. L., Gilson, J. C., and Wood, C. H.: Population studies of chronic respiratory disease. Br J Ind Med *16:*255-268, 1959.
49. Higgins, I. T. T., Gilson, J. C., Ferris, B. G. Jr., Waters, M. E., Campbell, H., and Higgins, M.: Chronic respiratory disease in an industrial town: a nine-year follow-up study. Prelminary Report. Am J Public Health *58:*1667-1676, 1968.
50. Higgins, I. T. T., Higgins, M. W., Lockshin, M. D., and Canale, N.: Chronic respiratory disease in mining communities in Marion County, West Virginia. Br J Ind Med *25:*165-175, 1968.
51. Hill, A. B.: Sickness amongst operatives in Lancashire cotton spinning mills (with special reference to the cardroom). Rep Indust Hlth Res Bd. Rep No. 59, London: HMSO 1-91, 1940.
52. Hirst, R. N. Jr., Perry, H. M. Jr., Crus, M. G. and Pierce, J. A.: Elevated cadmium concentration in emphysematous lungs. Am Rev Respir Dis *108:*30-39, 1973.
53. Hogg, J. C., Macklem, P. T. and Thrulbeck, W. M.: Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med *278:*1355-1360, 1968.
54. Holland, W. W. and Reid, D. D. The urban factor in chronic bronchitis. Lancet *1:* 445-448, 1965.
55. Howard, P.: A long-term follow-up of respiratory symptoms and ventilatory function in a group of working men. Br J Ind Med *27:*326-333, 1970.
56. Hyatt, R. E., Kistin, A. D., and Mahan, T. K.: Respiratory disease in southern West Virginia coal miners. Am Rev Respir Dis *89:*387-401, 1964.
57. Janoff, A.: Human granulocyte elastase: further delineation of its role in connective tissue damage. Am J Pathol *68:* 579-591, 1972.
58. Johanson, W. G. and Pierce, A. K.: Effects of elastase, collagenase and papain on structure and function of rats' lungs *in vitro.* J Clin Invest *51:*288-293, 1972.
59. Johnston, R. N., McNeill, R. S., Smith, C. H., Legg, J. S. and Fletcher, F.: Chronic bronchitis measurements and observations over 10 years. Thorax *31:*25-29, 1976.
60. Jorgensen, H. and Svensson, A.: Studies on pulmonary function and respiratory tract symptoms of workers in an iron ore mine where diesel trucks are used underground. JOM *12:*348-354, 1970.
61. Karpick, R. J., Pratt, P. C., Asmundsson, T., and Kilburn, K. H.: Pathological findings in respiratory failure, goblet cell metaplasia, alveolar damage and myocar dial infarction. Ann Intern Med *72:*189-197, 1970.
62. Kazantsis, G., Flynn, F.V., Spowage, J.S. and Trott, D.G.: Renal tubular malfunction and pulmonary emphysema in cadmium pigment workers. Q J Med *32:* 165-192, 1963.
63. Kilburn, K.H. and Asmundsson, T.: Anteroposterior chest diameter in emphysema. JArch Intern Med *123:* 379—382, 1969.
64. Kilburn, K.H., Dowell, A.R., and Pratt, P.C.: Morphological and biochemical assessment of papain emphysema. Arch Intern Med *127:*884-890, 1971.
65. Lambert, P.M. and Reid, D.D.: Smoking, air pollution and bronchitis in Britain. Lancet *1:*853-857, 1970.
66. Lane, R.E. and Campbell, A.C.P.: Fatal emphysema in two men making a copper cadmium alloy. Br J Ind Med

*11:*118-122, 1954.
67. Leopold, J.G. and Gough, J.: The centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. Thorax *12:*219-235, 1957.
68. Lewis, G.P., Coughlin, L.L., Jusko, W.J., and Hartz, S.: Contribution of cigarette smoking to cadmium accumulation in man. Lancet *2:*291-292, 1972.
69. Lowe, C.R., Campbell, H., and Khosla, T.: Bronchitis in two integrated steel workers, respiratory symptoms and ventilatory capacity related to atmospheric pollution. Br J Ind Med *27:*121-129, 1970.
70. McLean, K.H.: Bronchiolitis and chronic lung disease. Br J Tuberc *52:*105-113, 1958.
71. McLean, K.H.: The pathogenesis of pulmonary edema. Am J Med *25:*62- 74, 1958.
72. Medical Research Council's Committee on the Aetiology of Chronic Bronchitis. Standardized questionnaires on respiratory symptoms. Br Med J *2:*1665, 1960.
73. Medvei, V.C. and Oswald, N.C.: Chronic bronchitis: a five year follow-up. Thorax *17:*1-4, 1962.
74. Merchant, J.A. and Kilburn, K.H. (unpublished data).
75. Merchant, J.A., Lumsden, J.C., Kilburn, K.H., O'Fallon, W.M., Ujda, J.R., Germino, V.H. Jr., and Hamilton, J.D.: Dose response studies in cotton textile workers. JOM *15:*222-230, 1973.
76. Milne, J.S.: Longitudinal respiratory studies in older people. Thorax *33:*547- 554, 1978.
77. Mitchell, R.S., Stanford, R.E., Johnson, J.M., Silvers, G.W., Dart, G., and George, M. S.: The morphologic features of the bronchi, bronchioles, and alveoli in chronic airway obstruction: a clinicopathologic study. Am Rev Respir Dis *114:*137-145, 1976.
78. Morgan, W.K.C.: Industrial bronchitis. Br J Ind Med *35:*285-291, 1978.
79. Morgan, W.K.C., Burgess, D.B., Jacobson, G., O'Brien, R.J., Pendergrass, E.P., Reger, R.B., and Shoub, F.P.: The prevalence of coalworkers' pneumoconiosis in US coal miners. Arch Environ Health *27:*221-226, 1973.
80. Morgan, W.K.C., Burgess, D.B., Lapp, N.L., Seaton, A., and Reger, R.B.: Hyperinflation of the lungs in coal miners. Thorax *26:*585-590, 1971.
81. Morrow, P.E., Gibb, F.R., and Gazioglu, K.M.: A study of particulate clearance from the human lungs. Am Rev Respir Dis *96:*1209-1221, 1967.
82. Musk, A.W., Peters, J.M., Wegman, D.H., and Fine, L. J.: Pulmonary function in granite dust exposure: a four-year follow-up. Am Rev Respir Dis *115:*769-776, 1977.
83. Naeye, R.L.: Structural features in Appalachian coal workers, in Pulmonary Reactions to Coal Dust, a Review of U.S. Experience, M.M. Key (ed.). New York: Academic Press, 93-110, 1971.
84. Nandi, M., Jick, H., Slone, D., and Shapiro, S.: Cadmium content of cigarettes. Lancet *2:*1332-1339, 1969.
85. National Institute for Occupational Safety and Health. Occupational Diseases. A Guide to Their Recognition. PHS Publication No. 1097. U.S. Public Health Service, Washington, DC., 1977.
86. Nicklaus, T.M. and Stowell, D.W.: The accuracy of the roentgenologic diagnosis of chronic pulmonary emphysema. Am Rev Respir Dis *93:*889-899, 1966.
87. Northway, W.H., Rosan, R. C., and Porter, D.Y.: Pulmonary disease following respiratory therapy of hyaline-membrane disease. N Engl J Med *276:*357-368, 1967.
88. O'Dell, B.L., Kilburn, K.H., McKenzie, W.N., and Thurston, R.J.: The lung of the copper deficient rat, a model of developmental pulmonary emphysema. Am J Pathol *91:*413-424, 1978.
89. Ortmeyer, C.E., Baier, E.J., and Crawford, G.M. Jr.: Life expectancy of Pennsylvania coal miners compensated for disability. Arch Environ Health *27:*227-230, 1973.
90. Oswald, N.C., Harold, J.T., and Martin, W.J.: Clinical pattern of chronic bronchitis. Lancet *2:*639-643, 1953.
91. Oswald, N.C., Medvei, V.C., and Waller, R.D.: Chronic bronchitis: a 10 year follow-up. Thorax *22:*279-285, 1967.
92. Passmore, R. and Robson, J.S.: A companion to medical studies. Vol. 111,.

Part I. Lippincott, 1974.
93. Peters, J.M. and Murphy, R.L.H.: Pulmonary toxicity of isocyanates. Ann Intern Med *73:*654-655, 1970.
94. Pratt, P.C. and Kilburn, K.H.: Extent of pulmonary pigmentation as an indicator of particulate environmental air pollution, in Inhaled Particles III, W.H. Walton (ed.). Surrey, England: Unwin Brothers, Ltd., 661-669, 1971.
95. Reid, D.D. and Fairbairn, A.S.: The natural history of chronic bronchitis. Lancet *1:*1147-1152, 1958.
96. Reid, L.M.: Correlation of certain bronchographic abnormalities seen in chronic bronchitis with the pathological changes. Thorax *10:*199-204, 1955.
97. Reid, L.M.: Measurement of the bronchila mucous gland layer: a diagnostic yardstick of chronic bronchitis. Thorax *15:*132-141, 1960.
98. Reid, W.D., Ilett, K. F., Glick, J.M., and Krishna, G.: Metabolism and binding of aromatic hydrocarbons in the lung: relationship to experimental bronchiolar necrosis. Am Rev Respir Dis *107:*539-551, 1973.
99. Renzetti, A.D. Jr., McClement, J.H., and Litt, B.D.: Veterans Administration cooperative study of pulmonary function III. Mortality in relation to respiratory function in chronic obstructive pulmonary disease. Am J Med J *41:*115-129, 1966.
100. Rogan, J. M., Attfield, M.D., Jacobsen, M., Rae, S., Walker, D.D., and Walton, W.H.: Role of dust in the working environment in development of chronic bronchitis in British coal miners. Br J Ind Med *30:*217-226, 1973.
101. Ryder, R., Lyons, J.P., Campbell, H., and Gough, J.: Emphysema in coal worker's pneumoconiosis. Br Med J *3:*481-487, 1970.
102. Ryder, R. C., Thurlbeck, W.M., and Gough, J.: A study of interobserver variation in the assessment of the amount of pulmonary emphysema in paper-mounted whole lung sections. Am Rev Respir Dis *99:*354-364, 1969.
103. Saric, M., Kalacic, I. and Holetic, A.: Follow-up of ventilatory lung function in a group of cement workers. Br J Ind Med *33:*18-24, 1976.
104. Scott, R., Mills, E.A., Fell, G.S., Husain, F.E.R., Yates, A.J., Paterson, P.J., McKirdy, A., Ottoway, J.M., Fitzgerald-Finch, O.P., and Lamont, A.: Clinical and biochemical abnormalities in coppersmiths exposure to cadmium. Lancet *2:*396-398, 1976.
105. Sharp, J.T., Oglesby, P., McKean, H., and Best, W.R.: A longitudinal study of bronchitic symptoms and spirometry in a middle-aged, male, industrial population. Am Rev Respir Dis *108:*1066- 1077, 1973.
106. Shaw, R.R., Paulson, D.L., and Kee, J. L. Jr.: Mucoid impaction of the bronchi. Am Rev Tuberc and Pul Dis *76:*970- 982, 1957.
107. Simon, G. and Galbraith, H.J.B.: Radiology of chronic bronchitis. Lancet *2:*850-852, 1953.
108. 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. Br J Ind Med *24:*1-12, 1967.
109. Smith, J.P., Smith, J.C., and McCall, A.J.: Chronic poisoning from cadmium fumes. J Pathol Bact *80:*287-296, 1960.
110. Smith, R. T. and Lilienfeld, A.M.: The Social Security Disability Program: an evaluation study, 1975. HEW Soc Sec Adm Res Rep 39, DHEW Pub. No. (SSA) 72-11801.
111. Smith, T.J., Thomas, L.P., Reading, J.C., and Lakshminarayan, S.: Pulmonary effects of chronic exposure to airborne cadmium. Am Rev Respir Dis *114:*161-169, 1976.
112. Snider, G.L., Hayes, J.A., Korthy, A.L., and Lewis, G.P. : Centrilobular emphysema experimentally induced by cadmium chloride aerosol. Am Rev Respir Dis *108:*40-47, 1973.
113. Sutin, A., Christoforidis, A.J., Klugh, G.A., and Pratt, P.C.: Roentgenologic criteria for the recognition of nonsymptomatic pulmonary emphysema. Correlation between roentgenologic findings and pulmonary pathology. Am Rev Respir Dis *91:*69-76, 1965.
114. Thurlbeck, W.M.: Chronic airflow obstruc-

tion in lung disease. Philadelphia: W.B. Saunders Co., p. 50, 1976.
115. Thurlbeck, W.M.: Goblet cells in the peripheral airways in chronic bronchitis. Am Rev Respir Dis *112:*65-69, 1975.
116. Tse, K.S., Warren, P., Janusz, M., McCarthy, D.S., and Cherniack, R.M.: Respiratory abnormalities in workers exposed to grain dust. Arch Environ Health *27:*74-77, 1973.
117. Vanderbergh, E., Clement, J., and Woestijne, K.P.: Course and prognosis of patients with advanced chronic obstructive pulmonary disease. Am J Med *55:*736-746, 1973.
118. Warner, C. G., Davies, G.M., Jones, J.G. and Lowe, C.R.: Bronchitis in two integrated steelworkers II. Sulphur dioxide and particulate atmospheric pollution in and around the two workers. Ann Occup Hyg *12:*151-170, 1969.
119. Wegman, D.H., Peters, J.M., Pagnotto,, L. and Fine, L.J.: Chronic pulmonary function loss from exposure to toluene diisocyanate. Br J Ind Med *34:*196-200, 1977.
120. Weiss, W. and Boucot, K.: The respiratory effects of chloromethyl methyl ether. JAMA *234:*1139-1142, 1975.
121. Worth, G., Muysers, K., Smidt, U., and Gasthaus, L.: The epidemiology of bronchopulmonary symptoms in coal miners, foundry workers, chemical workers and bakers. Bull Physio-path Resp *6:*617-636.
122. Wyatt, J.P.: General pathology, in Pulmonary Reactions to Coal Dust, M.M. Key, L.E. Kerr and M. Bundy (eds.) New York: Academic Press, 71-92, 1971.