Pathology of Pulmonary Disease, edited by Mario J. Saldana.
J. B. Lippincott Company, Philadelphia © 1994.

77

Environmental and Occupational Aspects of Pulmonary Disease

John E. Craighead

Man's recorded awareness of occupational lung disease began with the history of medicine and the writing of Hippocrates, who referred to the metal digger as a "man who breathes with difficulty."[1] It is likely that silicosis and asbestosis occurred before written history—early metal workers and those who honed flint were exposed to silica dust, and asbestos has been found in the wrappings of mummies and in early pottery artifacts. Pliny the Elder mentioned the use of respirators to avoid lung disease, as did Agricola, an early sixteenth-century physician who described pulmonary disease in miners. Paracelsus, an occupational physician employed by a smelter in the Tyrols, and who was later a professor of medicine in Basel, described cough, dyspnea, and cachexia in miners. However, the direct relationship of dust exposure to lung disease appears to have eluded these early physicians.

More modern studies of silicosis began with English physicians in the late 1700s who noted the association of silica dust exposure with the development of respiratory symptoms. The Industrial Revolution set the stage for an epidemic of dust-related diseases. The conditions were termed "Pneumokoniosis" by von Zenker (1825–1898), a pathologist. Asbestosis was first described in a postmortem study conducted in 1900 by Montague Murray, but understanding of this disease did not evolve until the late 1920s, when Gloyne first described the "curious bodies" now known as asbestos bodies.[1a] No doubt, asbestos lung disease was confused clinically with silicosis and other chronic pulmonary conditions. Since that time, knowledge of the vast array of pneumoconioses and other diseases of the lung related to occupational exposure has grown dramatically. An overview of this accumulated information is beyond the scope of this chapter. Clinical, epidemiologic, and pathologic work during the last half of this century has made it possible to understand the pathophysiology and pathogenesis of many pulmonary disease problems related to occupational exposure, and has resulted in quantitative information that allows determination of theoretic and practical thresholds of exposure for the protection of workers.

Appreciation of nonoccupational, environment-related pulmonary disease came much later. During the autumn of 1948, a meteorological inversion settled over the Monongahela River Valley mill town of Donora in southwestern Pennsylvania, trapping air pollutants for several days. Some 20 respiratory deaths were believed to have resulted, and hundreds of residents of the valley experienced the abrupt onset of respiratory illness. Shortly thereafter, a dense, polluted smog enveloped London for a period of weeks, also extracting a high death toll. Other similar outbreaks occurred on the Continent. These episodes, and the subsequent increasing concern of Americans with air pollution, were critical factors influencing the passage of the initial Clean Air Act of 1963 by the U.S. Congress. Since that time, an enormous body of information on air pollution worldwide has accumulated, and governments in most developed countries have promulgated countless regulations.

The most recent renewal of the Clean Air Act increases regulatory constraints and takes into consideration for the first time a new concern, acid rain.[1b] Nevertheless, a pall of ozone, particulates, photooxidants, and acid hydrocarbon effluents lingers over many major cities and distant rural areas today. As a result, new restrictions on urban vehicular traffic are either threatened or planned by the United States Environmental Protection Agency, and additional limitations on smokestack effluents are being imposed. Attention is now focused on controlling pollutants worldwide, in developed and undeveloped countries alike.

In this complex milieu, fundamental scientific research seems inadequate to the challenge of defining the risk of disease resulting from long- and short-term exposure to ambient and occupational

air pollutants. Thus far, studies on humans have been largely limited to retrospective epidemiologic surveillance of selected high-risk subsets of the population, with all of the pitfalls of multivariate analysis in a heterogeneous, mobile assembly of research subjects. Because of these factors, most current investigations of environmental disease are limited to correlations of exposure to air pollution with acute episodes of respiratory disease.

Surveys using the results of airway function studies and x-ray films are also used to assess occupational and environmental exposures, but these investigations are useless in anticipating the effects of subtle low-level exposures. How is the cause of an illness determined when functional and analytic measures of these often subtle conditions are virtually nonexistent, and pathologic changes specific to the disease have not been established? How are considerations of individual host susceptibility and the influences of preexisting diseases, such as asthma and chronic obstructive pulmonary disease (COPD) incoporated into the diagnosis?

Scientists invariably turn to experiments in animals in attempts to deal with these complexities, but in these studies, analysis of effects of respiratory pollutants also poses substantial problems. Although sophisticated means are available for assessing the functional effects of inhalants at relatively high concentrations in small animals, invariably questions arise regarding risk analysis based on cross-species comparisons and the extrapolation of data accumulated at high exposure concentrations to much lower dosages. Although the pathologic effects of specific pollutants at high concentrations may be definable in the laboratory, it has not yet been determined whether or not similar, but more subtle, lesions are manifest after low-level exposures as well. The answers to these questions are of critical public importance because the health of millions is at stake. On the other hand, if estimates of risk are too conservative and regulations consequently too severe, the unnecessary economic costs could be incalculable.

Some of the most significant societal concerns in the 1980s and 1990s have arisen from occupational exposure to toxic substances in the workplace. Of these, the diseases resulting from asbestos and silica exposure undoubtedly are the most vivid examples. To what extent can the tragic health problems consequent to heavy exposures to dusts in the workplace during past decades be transposed to an understanding of the effects of much lower dust concentrations today? These are not easy questions to answer. How does society regulate the responsible, controlled use of valuable industrial products that are recognized to be hazardous when inappropriately used? The U.S. Occupational Safety and Health Administration and the Environmental Protection Agency have done so *de facto* by promulgating highly restrictive regulations based on an amalgam of animal and epidemiologic information. Other governments have acted more conservatively.

In this context, I now turn to a consideration of the potential respiratory health risks for future generations that might result from long-term exposures to contemporary ambient and occupational air pollutants. In the sections that follow, I will summarize my views in a highly personal overview of future challenges for pathologists, and their possible role in contributing to the understanding of environmental and occupational pulmonary disease.

AIRWAY DISEASE

Our understanding of the health effects of cigarette smoke and environmental gaseous and particulate air pollutants has evolved dramatically during the past two decades. Physiologists can now document small airway disease functionally, and pathologists have developed tools to evaluate quantitatively the effects of pollutants on the airways. Some pathologists voice the opinion that fibrotic disease of the lower airways (*i.e.*, peribronchiolar fibrosis) results in obstructive functional phenomenology, but correlative epidemiologically oriented evidence based on physiologic and pathologic data is totally lacking. For example, there continues to be considerable controversy in the pathologic and clinical literature as to the potential role of cigarette smoking in the production of fibrosis in the walls of the respiratory and membranous bronchioles. The research problems inherent in scientifically evaluating these questions are imposing, but they are at the heart of the pathologist's ability to interpret pulmonary histopathologic changes in the context of the patient. Additional attempts must be made to correlate experimental information with observations in humans whose smoking and environmental backgrounds are known. Until these questions are addressed creatively, pathologists will not be in a position to contribute meaningfully to the understanding of small airway disease (see Chap. 30).

At the level of the large bronchus, the histologic changes initially described by Reid in COPD are increasingly rare, most probably because of the substantial reduction in tobacco product abuse by many populations in the developed world, concomitant with improvements in air quality (see Chap. 27). However, the upper airways of members of the population remain to be examined critically by pathologists in a systematic fashion to determine whether or not diseases of the large airways develop in nonsmokers exposed to low concentrations of occupational and environmental pollutants.

In the occupational setting, humans are sporadically exposed to the fumes of chemicals, such as chlorine and ammonium, that have short-term toxic effects of dramatic importance when exposures are acute and extreme. Although most exposures to these chemicals are transient, several clinical reports suggest that even brief exposures can occasionally result in chronic airway obstructive disease (see Chap. 17). Brooks and his colleagues have described reactive airway dysfunction syndrome, in which pulmonary obstruction disease develops and symptomatic airway hyperactivity persists over extended periods consequent to acute exposures to highly irritating inhalants.[2] Clinicians believe that disease exhibited by a certain number of their patients fits the criteria established by Brooks,[2] but little, if anything, has been learned about the pathologic changes that occur in the lung tissue in such syndromes.

Occupational asthma is a syndrome that also defies pathologic interpretation, yet it is one of the most common forms of occupational disease and can be attributed to a wide variety of exposures in the workplace. The pathogenesis is far from clear, and the impact of the occupational inhalant on the airways of the smoker and those with respiratory infections is significant but poorly understood. These problems, too, are challenges for future generations of pulmonologists and pathologists (see Chap. 17).

A compelling body of new epidemiologic information suggests that the concentrations of ozone found in some urban environments have measurable effects on human pulmonary function. Data accumulated largely in experimental animals indicate that SO_2 and NO_2 affect airway function and produce interstitial pulmonary disease. The site of impact of ozone and other gases in humans would appear to be the respiratory bronchioles, but the pathologist has yet to define this effect morphologically in man and to correlate experimental animal observations with pathologic findings in humans. The enormous difficulty in accomplishing

this goal cannot be underestimated; it is possible that techniques currently available to the pathologist are inadequate for the challenge.

HYPERSENSITIVITY DISORDERS

Despite generations of research, little or no understanding of the etiology or mechanisms involved in the development of sarcoidosis is present. Is it, in fact, an environmental disease? New approaches to investigating this serious and widespread condition are sorely needed. The immunopathologist with an interest in pulmonary disease is in an ideal situation to investigate sarcoidosis with modern research tools. Correlative studies with epidemiologists are mandatory. Perhaps model systems can be developed as new immunologic techniques become available to quantitate human exposure to possible etiologic agents. There may, in fact, be a wide variety of substances similar to beryllium in the environment that could play a pathogenetic role in producing granulomatous pulmonary disease (see Chap. 66).

Hard metal disease, a condition allegedly due to exposure to cobalt complexed with hard metal particulates, may be an example. I have become particularly interested in this syndrome as I consult on sporadic cases of giant cell pneumonitis, a lesion well known to pulmonary pathologists. In hard metal disease, I suspect cobalt is the inciting agent, but the role of the small hard metal particulate is totally unclear. The possibility that cobalt annealed to these inert dust particulates sensitizes the patient to an unknown "self" or foreign antigen seems an appropriate departure for new study. If this is the case, what are the mechanisms of sensitization that result in profound restrictive lung disease in only a small proportion of the individuals exposed to hard metal dusts in the workplace? Are genetic factors involved? What is the pathogenesis of the giant cell lesion that characterizes this form of interstitial pulmonary disease (see Chaps. 17 and 37)?

Scleroderma continues to be a poorly understood multisystem disease process that can result in severe interstitial fibrosis. Hints as to the development of this condition have grown out of comprehensive evaluations of the long-term effects of silica dust exposure. In a number of epidemiologic studies, an increased prevalence of scleroderma and rheumatoid arthritis has been noted in individuals with advanced silicosis (see Chap. 35).[3] Is this disorder of immune regulation truly related to silica dust exposure? And, if so, what is the pathogenesis of the disease? Clinical evidence has accumulated suggesting that scleroderma may also develop in women with mammary silicone gel implants.[3a,3b] This observation is tantalizing in light of findings in the silicotic individuals referred to previously. How does silicone gel incite the development of scleroderma, if, in fact, it does? At present, the epidemiologic evidence necessary to be certain about the association is lacking; there is little or no understanding of the host factors involved. And, if the association, in fact, exists, we can only speculate regarding the pathogenetic mechanisms involved. Many would suggest that scleroderma in these cases results from the systemic activation of macrophages by silica dust and silicone gel. In women with ruptured or leaking mammary implants, silicone gel apparently is distributed throughout the body. Obviously, much remains to be learned.

Hypersensitivity pneumonitis in its most obvious form is a devastating progressive interstitial inflammatory and fibrotic process, but a spectrum of less severe, although similar, disease processes exists. The morphologic criteria for the diagnosis of hypersensitivity pneumonitis in its classical form are well known to pathologists, but it is likely that many cases go unrecognized because the typical clinical and pathologic features are not recognized. Despite intensive investigation by many immunopathologists, the pathogenesis of the disease is unclear. Some believe that it is consequent to cellular immune mechanisms, whereas there is also evidence to suggest that it is a humorally mediated disease process. It may be due to both types of immune processes. Antibodies directed against several thermophilic actinomyces (*i.e.*, common hay molds) usually are demonstrable in the blood serum of patients with farmers' lung syndrome, but serologic surveys have detected a significant number of serum antibodies in farmers who lack symptoms of the disease. Thus, sensitization does not necessarily result in disease, and serologic studies cannot be used to screen for disease. It is likely that genetic factors play a role in its pathogenesis, but these influences remain to be defined. In part, the confusion relates to the definition of the disease, clinically and pathologically. From an epidemiologic perspective, it may well be that many of the antigens in the environment that play a role in this hypersensitivity disorder have yet to be identified. Many problems amenable to imaginative research and potential resolution remain within the broad category of conditions nominally termed hypersensitivity pneumonitis. Because of the sporadic occurrence and variable features of this disorder, research has progressed slowly. Animal models have not been developed, which is another impediment to progress in understanding of this group of diseases (see Chap. 65).

Eosinophilic pneumonia and bronchiocentric granulomatosis represent two poles of a spectrum of hypersensitivity disorders that are presumably related to environmental exposure but are ill-defined from a pathogenetic point of view. The cause of the morphologically similar Löffler syndrome is understood, at least in part, from an etiologic perspective, but the specific causes of the other members of this broad complex of vaguely defined disease conditions remain uncertain. Pulmonary pathologists have directed considerable attention to defining these diseases morphologically, but their work has provided little insight into causation. Like so many other hypersensitivity conditions, heritable factors probably play a role, and the sporadic occurrences of the disease makes the work of those concerned with its etiology and pathogenesis exceedingly difficult. Yet subtle, environmental exposures to immunogens seem a plausible explanation for this group of disorders (see Chaps. 63 and 64).

ASBESTOS-ASSOCIATED DISEASES

No subject in the modern environmental and occupational literature has commanded more attention than the health risks related to asbestos. Yet few of the critical questions have been resolved despite considerable research. I will discuss below the issues as I am aware of them.

Pathologists have yet to agree on an acceptable definition of asbestosis as diagnosed microscopically. The criteria established by the College of American Pathologists and published in 1982 have been criticized by various parties.[4] It is appropriate to emphasize that these criteria are based on the presence of asbestos bodies and their association with tissues undergoing fibrotic change. At best, this is a crude criterion of disease, because numerous inhalants other than asbestos can cause lesions of the respiratory bronchioles. Clearly, more refined diagnostic approaches are needed. Numerous attempts have been made to associate the numbers of

asbestos bodies in tissue and the numbers of fibers detected by electron microscopy after digestion of lung tissue with the occurrence of disease. These studies have failed. Thus, it is not possible to use quantitative criteria for the diagnosis of the disease. Several publications have suggested that host factors influence the development of the lesions of asbestosis, and certainly cigarette smoking accelerates the appearance of the radiologic features of the disease.

Questions arise as to the potential fibrogenicity of different types of asbestos, but they have not been satisfactorily answered. Should differences, in fact, exist, this would further argue against the notion that the presence of asbestos bodies can be used as a criterion of disease, because some types (*i.e.*, chrysotile) produce asbestos bodies less often than others (*i.e.*, the amphiboles). However, little is known about why these bodies form and the whereabouts of the predominant numbers of fibers that do not develop into bodies. Do these fibers that lodge in the lung after exposure ceases cause progressive disease consequent to their presence? Clinicians are generally of the opinion that asbestosis progresses, but the evidence is sparse. Some would have us believe that immunologic factors initiated by the asbestos provoke the deposition of fibrous tissues. If so, avenues are open for new therapeutic approaches. None of these issues have been satisfactorily resolved. On the other hand, a considerable body of experimental information provides insights into the pathogenetic mechanism of pulmonary fibrosis, and attempts to prevent the development of the disease in experimental models have succeeded (see Chap. 36).[5]

No subject is more contentious than questions related to the possible role of asbestos in the pathogenesis of bronchogenic carcinoma.[6] Some experimental and epidemiologic findings support the notion that asbestos is, in fact, a carcinogen in the respiratory tract. Alternatively, experimental evidence argues that asbestos serves as a promoter substance. This question is critical but remains unresolved. Epidemiologic studies suggest that dosage considerations are important; they have shown that the prevalence of bronchogenic carcinoma among smokers is not increased until asbestosis exists, as determined histologically and by radiologic criteria. This would indicate that there is a threshold of exposure under which asbestos does not cause cancer (see Chap. 36).

Much emphasis has focused on the ability of asbestos and other inhalants to induce adenomas and adenocarcinomas in the lungs of experimental animals. Indeed, this criterion has been used by governmental regulators as a tool for evaluating the carcinogenicity of respiratory inhalants of many different types. Morphologically, the lesions developing in the lungs of lesser animal species exposed to asbestos only superficially resemble human bronchogenic carcinomas histologically. Moreover, the lesions do not develop in all strains of animals experimentally exposed. Thus, genetic factors critically influence their occurrence. Clearly, there is a need for more insightful approaches to the identification of respiratory carcinogens in the environment.

The pathogenesis of mesothelioma in humans is far from clear.[7] A substantial majority of the cases appear to result from exposure to amphibole asbestos, but debate continues with regard to the role of chrysotile asbestos in the causation of malignant mesothelioma. Chrysotile is substantially less carcinogenic than the amphiboles, but some qualified investigators argue that, at high dosages and over a prolonged period of exposure, chrysotile can, in fact, initiate the development of mesothelioma. But the epidemiologic evidence is limited. Tremolite, a common contaminant of chrysotile, also has been implicated in the causation of these tumors, but its role in the disease has not been established. These questions are of critical public health and economic importance, because asbestos is a relatively inexpensive, useful insulation material and fire retardant.

Mesotheliomas develop in individuals who have no documented occupational or avocational exposure to asbestos. Some believe that the low concentrations of asbestos found in the ambient air of cities and public buildings may play a role in the development of disease in these individuals. However, the epidemiologic evidence is inconsistent with this viewpoint because spontaneously developing mesotheliomas occur in children and teenagers, as well as in relatively young adults. Accordingly, it must be asked what factors other than asbestos can initiate the development of mesotheliomas. Are they environmental (see Chap. 57)?

The pathogenesis of mesothelioma at the molecular and cellular level is far from clear. Abundant experimental evidence suggests that mesotheliomas uniquely result from exposure to relatively long fibers, not the short fibers that predominate in commercial products. If so, what is unique about the long fibers? There is no evidence to indicate that oncogene amplification or specific mutations at the molecular or chromosomal level are responsible. No information exists as to cellular events during the long latency periods of these tumors from the time of exposure to the development of the disease. In contrast to most cancers, mesotheliomas usually lack the capability to invade tissue and customarily grow only into nearby tissues such as the lung, and they metastasize widely, late in the course of the disease. The biologic basis for these features is unclear.

Plaques and visceral pleural fibrosis are uniquely associated with exposure to asbestos. Their pathogenesis, however, is obscure. Pleural plaques develop frequently in those whose exposure is insufficient to cause asbestosis. Thus, they are a sensitive measure of low-level exposure. Pleural fibrosis occurs less frequently, but when it does, the lesions can prove dramatic. Experimental evidence suggests that growth factors generated by macrophages may play a role in the development of these striking fibrotic lesions, but the evidence to support such a notion is limited. Clearly, opportunities exist for imaginative research with the use of modern cellular and molecular approaches.

SILICA-RELATED DISEASE

Although silicosis can be viewed as a disappearing disease, the pathogenesis of the characteristic silicotic nodule is far from clear. This unique lesion consists of a spherical, circumscribed whorled mass of hyalinized collagenous tissue. How does it develop, and how does the small amount of silica found in the center of these nodules cause the lesion? Are growth factors or immunologic mechanisms involved in the genesis of these progressive lesions? In many mineral deposits, silica is associated with a variety of silicates and carbonaceous material, such as coal, feldspar, and muscovite. A considerable body of evidence suggests that these relatively nonfibrogenic particulates that accompany the silica dust decrease its pathogenicity and ability to cause lesions in tissue. If so, how do these materials act to alter the effects of silica? This question is also unresolved.

As with asbestos, the role of silica in the pathogenesis of

bronchogenic carcinoma is debated.[3,6] Unfortunately, much of the accumulated evidence is based on epidemiologic observations in which such critical cofactors as cigarette smoking and ancillary exposures to known carcinogens have not been excluded. Therefore, the results of many studies must be discounted. Some critical work has been carried out, however, in which efforts were made to define the role of cigarette smoking in conjunction with silica exposure. Unfortunately, the reported studies differ in their conclusions. One investigation from South Africa suggests that the prevalence of bronchogenic carcinoma in the silica-exposed nonsmoker is increased when and if nodular lesions are present in hilar or mediastinal lymph nodes.[6] Additional studies have suggested that the increase is observed only when the exposure is of sufficient severity and duration to result in clinical silicosis. Yet the scientific basis for this conclusion and the mechanism whereby silica causes neoplasia are unclear. Several laboratories are pursuing these questions with the use of experimental models, but do the adenomas and adenocarcinomas they produce in animals satisfactorily simulate human lung cancer (see Chap. 35)?

Talc is an economically important mineral scattered in deposits throughout the earth. The characteristics of each talc product seem to differ mineralogically from the next, including the minerals found within them. Thus, contaminants of talc retained in the lungs of exposed individuals can serve as fingerprints, often allowing the specific identification of the source of the talc. Talcosis has distinctive pathogenetic features.[8] I conjecture, but have not proved, that this condition develops when the clearance mechanisms of the airways are overwhelmed with foreign particulates. Although the particulates are not highly cytotoxic, they have the ability to elicit, by unknown mechanisms, an interstitial fibrotic process that is centered primarily around the lymphatics that accompany bronchi and vessels throughout the lungs. It is not certain how and under what circumstances granular or platy silicate particulates accumulate adjacent to lymphatics throughout the lung to elicit interstitial fibrosis. The typical pathognomonic lesion of silicate dust exposure, therefore, is unexplained from the point of view of the mechanism whereby it develops.[9]

I have often observed peribronchial and perivascular fibrotic lesions similar to the lesions of talcosis in the lungs of individuals undergoing routine autopsy. X-ray spectrometry provides a means to identify and characterize the dust deposits, which often are found to be fibrous and granular aluminum silicates such as kaolin, feldspar, and mica. In my view, the pathologist is obliged to pursue aggressively information as to the source of the exposure to the dusts, if insights into the environmental causes of the disease are to be accumulated. Opportunities still clearly exist for defining the origin of environmental disease.

LUNG CANCER

The possible role of asbestos and silica in the pathogenesis of bronchogenic carcinoma was discussed previously. Little new can be said about the role of cigarette smoking in the causation of bronchogenic carcinoma, but it should be emphasized that the mechanisms whereby tobacco smoke produces cancer are only vaguely defined in constructs developed from experimental information. There is still no explanation why so many heavy smokers fail to develop lung carcinoma. In some respects, this is a more interesting scientific question than how cancer develops as a result of cigarette smoke exposure. Do genetic factors play a role, or are dietary and other environmental considerations important? Epidemiologic evidence now suggests that certain constituents of diet, particularly those containing vitamin A and carotene, protect against the development of lung cancer, but other substances, such as antioxidants in environment or diet, also may play a role (see Chap. 46). Clearly, additional research should focus on the reasons why cancer fails to develop in many heavy smokers.

A significant proportion of older persons with bronchogenic carcinoma do not have histories of cigarette smoking. Almost one half of women older than 50 years of age with adenocarcinoma have not smoked. What is the pathogenesis of this form of lung cancer? Does it relate to an environmental exposure too subtle to recognize, such as sidestream smoking or environmental exposure to radon? Careful, correlative epidemiologic and pathological studies are needed to address these questions (see Chap. 47). Abundant evidence seems to indicate that radon either plays a direct carcinogenic role or serves as a cocarcinogen with cigarette smoke in the causation of bronchogenic carcinoma. If so, how can these lesions be detected and differentiated from those induced by cigarette smoking? Studies using biomarkers of exposure provide one possible answer, but scientific research in future years no doubt will yield others.

Emphysema of a centrilobular distribution is customarily thought to be the major lung parenchymal effect of cigarette smoking. As discussed previously, abundant evidence suggests that interstitial fibrosis in the respiratory bronchioles also is caused by cigarette smoke, often in association with pollutants in the environment of the industrialized community.[10,11] Yet emphysema occurs in a relatively small proportion of heavy smokers, and the peribronchiolar fibrosis suspected to be related to cigarette smoking often occurs in the absence of emphysema. What factors influence the development of these quite different lesions? Undoubtedly, host influences are important, and air pollutants other than cigarette smoking may be important. In a fascinating study, lathyritic agents administered to animals in association with a fibrosing agent (*i.e.*, cadmium chloride) were shown to produce emphysematous dilatation of the air spaces of the lungs similar to that observed in cigarette smokers, but emphysema did not occur in cadmium-exposed animals in the absence of the lathyrogen.[12] Some lathyritic agents are present in the human diet, but it is unlikely that they are a significant cause or cofactor in human lung disease. However, other chemicals, as yet unrecognized, may play a similar role. Could the development of emphysema reflect the interaction of several different cofactors, including heritable influences in the smoker? The question is addressable despite the complexities of conducting studies in humans (see Chap. 26).

Indoor air pollution is an increasingly important consideration as more and more of our population spend a substantial proportion of their time in fully air-conditioned, closed quarters, for both work and recreation.[13,14] The health hazards evaluations carried out by the National Institute for Occupational Safety and Health have disclosed large numbers of sick buildings scattered throughout the country. Tobacco smoke, formaldehyde, and a variety of other organic volatiles released in small quantities into airtight buildings appear to play a role in the development of the complex montage of generalized symptoms that relate only in part to irritation of the mucous membranes of the respiratory tract. Are the effects of this disease syndrome reflected in structural changes in the lungs demonstrable by traditional morphologic techniques,

or must pathologists develop new approaches to understanding this disease process?

Acid rain continues to perplex environmentalists. Some suggest, as the recent Congressional Commission indicated,[15] that acid rain is of limited health importance and manifests its effects on the biota of only a few rare lakes or on scattered mountain peaks in the eastern United States. Many question this conclusion and suggest that the acids and other effluents of carbonaceous fuel combustion in acid rain have an adverse effect on the respiratory tract. Chronic inhalation of toxic acid-containing particulates in the air no doubt affects the respiratory epithelium, but it is difficult to assess critically whether or not health problems result. If acid rain and acid aerosols have the potential for eroding permanent structures such as statues and architectural iron work (Color Fig. 77-1), it seems probable that they have an effect, however subtle, on the respiratory epithelium of humans. Will pathologists in the future address this question?

REFERENCES

1. Hunter D. The diseases of occupations. 6th ed. London: Hoddes & Stoughton, 1978:1.

1a. Craighead JE, Juliano EB. Asbestos-associated diseases: can the issues be resolved in the courtroom? In: DG Scarpelli, JE Craighead, N Kaufman, eds. The pathology and the environment. IAP Monograph No. 26. Baltimore: Williams and Wilkins, 1985:211.

1b. Clean Air Act, Amendments. Public law No. 101-549; November 15, 1990. In: United States Code Congressional News. One hundred and first Congress, second session. St. Paul, MN: West Publishing, 1990.

2. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent airways hyperreactivity after high level irritant exposure. Chest 1985;88:376.

3. Craighead JE, Kleinerman J, Abraham JL, et al. Diseases associated with exposure to silica and nonfibrous silicate minerals. Arch Pathol Lab Med 1988;112:673.

3a. Varga J, Schumacher HR, Jimenez SA. Systemic sclerosis after augmentation mammoplasty with silicone implants. Ann Intern Med 1989;111:377.

3b. Sahn EE, Garen PD, Silver RM, Maize JC. Scleroderma following augmentation mammoplasty: report of a case and review of the literature. Arch Dermatol 1990;126:1220.

4. Craighead JE, Abraham JL, Churg A, et al. The pathology of asbestos-associated diseases of the lungs and pleural cavities: diagnostic criteria and proposed grading schema. Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. Arch Pathol Lab Med 1982;106:542.

5. Mossman BT, Marsh JP, Gilbert R, et al. Development and characterization of rapid-onset inhalation model of asbestosis in rats. Toxicol Pathol 1992;19:412.

6. Craighead JE. Do silica and asbestos cause lung cancer? Arch Pathol Lab Med 1992;116:16.

7. Craighead JE. Current pathogenetic concepts of diffuse malignant mesothelioma. Hum Pathol 1987;28:544.

8. Vallyathan NV, Craighead JE. Pulmonary pathology of workers exposed to non-asbestiform talc. Hum Pathol 1981;12:18.

9. Bignon J, ed. Health related effects of phyllosilicates. Berlin: Springer-Verlag, 1990.

10. American Thoracic Society. Report of the ATS Workshop on Environmental Controls and Lung Disease, Santa Fe, NM, March 24–26, 1988. Am Rev Respir Dis 1990;142:915.

11. Goldstein RA, Craighead JE. Summary of Work Group on Lung Disease: proceedings of Workshop on Chronic Disease in the Workplace and the Environment. Arch Environ Health 1984;39:249.

12. Niewoehner DE, Hoidal JR. Lung fibrosis and emphysema: divergent responses to a common injury? Science 1982;217:359.

13. Samet JM, Marbury MC, Spengler JD. State of art: health effects and sources of indoor air pollution. Part II. Am Rev Respir Dis 1988; 137:221.

14. Letz GA. Sick building syndrome: acute illness among office workers—the role of building ventilation, airborne contaminants and work stress. Allergy Proc 1990;11:109.

15. National Acid Precipitation Assessment Task Force. National Acid Precipitation Assessment Program Key Results. Washington, DC, National Academy of Sciences, 1990.