COAL WORKERS' PNEUMOCONIOSIS

F. H. Y. GREEN AND W. A. LAQUEUR

An excess of pulmonary disease has been recognized in coal workers for over 150 years. However, the characteristic lesions were not described until the middle of this century when techniques became available for the examination of whole lung sections. The term coal workers' pneumoconiosis (CWP) was introduced by the Committee on Industrial Pulmonary Disease of the Medical Research Council of Great Britain in 1942.[1] It was carefully chosen to avoid any etiologic implications, particularly in regard to the role of silica in the pathogenesis of the disease. The term is now universally accepted and will be used throughout this article. It is not our intention to give a detailed account of the history of CWP. Several excellent articles tracing the social, economic, political, and medical aspects of the disease have been published elsewhere. The reader is referred to the classical works of Meiklejohn in England,[2] Klosterkotter in Germany,[3] and Lee in the United States [4] for this information.

The purpose of this article is threefold: first, to review the current state of knowledge of the pathology of coal workers' pneumoconiosis and to relate this to the information derived from radiologic and clinical studies; second, to illustrate the various pulmonary lesions that are thought to be causally related to the inhalation of coal mine dust; and third, to discuss those aspects of CWP which have generated the most controversy and confusion within the medical profession.

The material presented here is based on the two largest collections of autopsy material on underground coal workers available in the United States today. This includes the 2,400 cases submitted to the National Coal Workers Autopsy Study since its inception in 1971 [5] and a unique collection of 700 cases from Southern West Virginia. The classification of the roentgenograms illustrated in this article is based on the UICC/Cincinnati system. A summary outline of the classification is shown in the Appendix.

COAL AND COAL MINING

Some knowledge of mining methods and the composition of coal mine dust is necessary to understand the pathogenesis of CWP. In the United States, four types of coal are mined; these are, in order of rank and economic value, anthracite, bituminous, subbituminous, and lignite. Higher-ranked coals contain the most carbon, have the greatest caloric value, and contain the least volatile matter.[6] The differences between one coal and another are due to the conditions prevailing when the coal seams were laid down and the nature of the plants that formed the coals. Subsequent weathering and seepage from adjacent rock strata may alter the con-

centrations of minerals in the coals. Anthracite is derived mainly from northeastern Pennsylvania; bituminous and subbituminous coals from Appalachia, the Mid- and Far West; and lignite is found in the Dakotas.[7] The height of the seams and their inclinations vary greatly. The thinnest seams are found in Appalachia, where they average 5 to 6 feet thick but may be as little as 1½ feet; in Colorado and Utah, seams up to 100 feet thick are encountered.[8] The seams of bituminous coal are usually horizontal, whereas anthracite coal lies in seams that gently undulate.

The methods by which different coals are mined may affect the composition of the coal mine dust. Anthracite mining requires the removal of large quantities of intervening rock as well as the use of sand on the train rails for traction; as a result, exposure to free silica may be increased. Certain occupations within the mines such as roofbolting, locomotive operation, and construction are also associated with increased exposure to crystalline silica,[7] and miners employed in these jobs may develop classical silicosis. The majority of the dust in the mines is generated at the coal face, and the operators of the cutting and loading machines are exposed to the highest concentrations.[7, 9] Studies conducted by the Bureau of Mines in 1968 and 1969 on 29 large and 12 small underground mines showed the average concentration of respirable dust at the face in both large and small mines was approximately 4.0 mg per cubic meter of air (m^3).[7] The quartz content of the dust in the large mines was always below 5 percent, with an average of 1.5 percent. Respirable dust exposures are lower in surface mining facilities,[7] and this probably accounts for the low incidence of pneumoconiosis detectable in workers at these sites.[10]

Mandatory Dust Standards

The Federal Coal Mine Health and Safety Act of 1969 established permissible levels of respirable dust in underground coal mines.[5] Since 1972 this limit has been set at 2.0 mg/m^3, and the quartz content in the dust must not exceed 5 percent. Standard conditions of dust sampling are set forth in the Code of Federal Regulations, Title 30, Parts 70 and 71. The 2.0 mg/m^3 dust standard was based on chest roentgenographic studies of British coal miners.[11] These studies indicated that if the coal dust exposures were maintained at or below this level, the probability of a miner developing category II or greater pneumoconiosis during a worklife of 35 years would be zero.

Respirable Dust

Respirable coal mine dust is a complex mixture of particulates of various sizes and shapes which are derived from the coal seam, the adjacent rock strata, the rock dust used to prevent explosions, and in some mines, diesel particulates. Therefore, it usually contains a greater ash content than the parent seam.[12] Coal is

composed predominantly of elemental carbon, together with varying amounts of a large number of minerals, metals, and organic compounds. The most common minerals in coal are pyrite, quartz, calcite, calcium sulfate, dolomite, siderite, and magnetite, as well as a variety of micas and other silicates.[12-17] The amount of quartz (SiO_2) in coal varies from 1 to 5 percent but may be much higher in the coal mine dust.[14] The most common metals in coal are aluminum, calcium, iron, magnesium, potassium, and sodium, with lesser amounts of beryllium, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickle, and titanium.[12,15] Many of these metals are known carcinogens. Organic compounds include a variety of gases, benzenes, phenols, naphthalenes, acenaphthylenes, and three-, four-, and five-ring polynuclear aromatic hydrocarbons and their alkyl homologs.[18] Coal mine dust is not the only respiratory hazard in mines. Electrical fires,[18] welding, and/or brazing operations may produce highly toxic fumes. Diesel emissions produce multifold organic substances and gases,[19] and shot firing releases oxides of nitrogen into the atmosphere.[20]

Deposition and Clearance of Inhaled Particles

The majority of particles deposited distal to the terminal bronchioles measure less than 10 μm in diameter. Particles greater than this are mainly filtered out in the nasal passages or are impacted on the surface of large airways. Inhaled particles within the respirable range are deposited on the airway surface by four mechanisms: inertial impaction, diffusion, gravitational settling, and interception.[21] The amount of dust deposited will depend on such physical factors as the concentration and physical characteristics of the respirable dust, the tendency of particles to agglomerate, and their electrical charge.[22] Host factors such as the breathing pattern of the miner and individual variation in particle deposition will also affect the amount deposited.[23, 24]

Inhaled dust particles may be cleared by one of three routes: the blood stream, the lymphatic system, or by the bronchial tree.[25, 26] Most of the dust deposited proximal to the respiratory bronchioles is cleared by the highly effective mucociliary stream which is propelled by ciliary activity. Several agents have been shown to either inhibit or stimulate this system. Inhibitors include cigarette smoke [27] and physiologic agents such as atropine.[27] Stimulators include the gases [28] SO_2 and NO_2 and the adrenergic stimulating drugs isoproterenol and epinephrine.[27] The rate of clearance is further influenced by the type of particle, whether it be inert, toxic, or organic in nature.[29]

Alveolar clearance is less well understood but appears to involve a vehicle and propelling force.[27] The majority of inhaled particles deposited in the alveoli are rapidly taken up by alveolar macrophages. These cells are thought to migrate over the airspace surface to the terminal bronchioles, where they enter the mucociliary stream.[26, 30] Although the vast majority of particles are removed by these mechanisms, a small proportion, perhaps less than 2 percent, will penetrate the airway lining and enter the interstitium.[26] Dust deposited in the interstitium is

the root cause of pneumoconiosis. Several tracer systems have been used to study the transport of particulates across the epithelium. Leak [31] showed that colloidal ferritin or carbon particles instilled into the lungs of rats and mice were rapidly taken up by alveolar macrophages and by the squamous alveolar epithelial cells (Type I pneumocytes). Within 2 hours, particles were observed in the alveolar interstitium and within phagocytic vacuoles of lymphatic endothelial cells; at 24 hours, they were detected in peribronchial lymphatics and lymph nodes. The passage of particulates through the alveolar epithelium has also been observed in mice exposed to iron oxide particles [32] and coal workers.[33]

Particles of different chemical composition may be cleared at different rates. The clearance of coal dust containing 40 percent quartz was studied in rats and Rhesus monkeys by Weller and Ulmer.[34] They showed that dust retention in the lung and lymph nodes increased linearly with exposure. On cessation of exposure, the dust in the lungs declined, while that in the lymph nodes continued to increase. This increase was largely due to quartz, suggesting that quartz is preferentially taken up by the pulmonary lymphatics. The pulmonary lymph nodes of coal workers also appear to concentrate silica,[35] which may account for the high frequency of silicotic nodules seen in the hilar lymph nodes of coal workers in the absence of parenchymal involvement.

The routes of lymphatic drainage of the lung have been extensively studied. Only recently was it clearly shown that lymphatic vessels exist at the alveolar level adjacent to the respiratory bronchioles (Fig. 1).[31, 36] This is an important observation, since it has been postulated that destruction or blockage of the lymphatic vessels in this area is the primary event in the formation of the coal macule.[30] Elimination of particles from the lungs continues for many years after last exposure. Even dust that is apparently locked in the areas of fibrosis is slowly mobilized and removed. Heppleston [37] has shown experimentally that the dust within silicotic lesions is in a continual state of flux, with particulate entering and leaving lesions within macrophages. The mobilized dust is mostly removed by the lymphatic system and deposited in the hilar lymph nodes. Nevertheless, the observation that coal miners continue to expectorate black or brownish sputum long after leaving the mines [26] suggests that dust may also be cleared in retrograde fashion from interstitium to air space. The extent to which this latter process occurs under physiologic conditions is not known, but is probably slight. Our review of many cases indicates that the pigment visible in the lesions remains fairly constant unless the miner has suffered repeated episodes of pulmonary congestion or edema. Increased clearance of dust has also been documented in experimental pulmonary edema.[38]

The rate of retention of coal mine dust in the lungs of miners has been calculated by Rivers et al.[39] They estimated that 0.1 to 3.7 gm of dust were retained by the lungs per year. This wide range probably reflects individual variations in clearance capacity, as the age of the miner and the length of time worked underground did not appear to influence the rate to any significant degree. Similar results were obtained by King et al.,[40] who calculated that an active coal worker on average retained about 1 gm of dust per year. This represents a very small fraction of the total dust inhaled and emphasizes the efficiency of the clearance mechanisms.

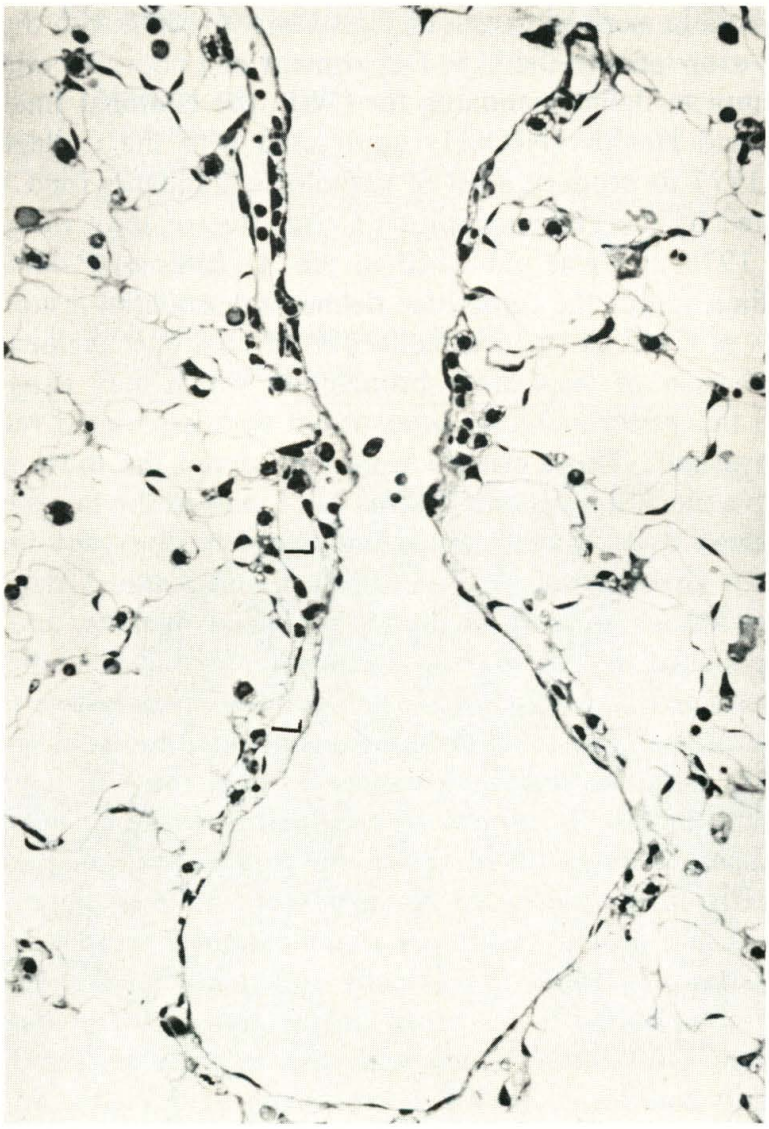


FIG. 1. Lymphatics (L) within the connective tissue sheath of a respiratory bronchiole which are in close apposition to alveoli. ×360. From LV Leak. In JD Brain, DF Proctor, LM Reid (eds): Respiratory Defence Mechanisms, Part II, 1977, p 643, by courtesy of Marcel Dekker, Inc.

PATHOLOGY OF CWP

The framework for our current understanding of the pathologic anatomy of CWP is largely due to the careful descriptive works of Heppleston [41] and Gough et al.[42] and to the development of techniques for examining lungs that have been fixed in inflation. Despite these and subsequent studies in the United States and other countries, there is still considerable confusion concerning the nomenclature of the disease. Analysis of the first 1,300 cases entered into the National Coal Workers Autopsy Study between 1971 and 1974 showed that pathologists could find 163 different ways to describe the lesions of CWP! (J. L. Abraham, personal communication) Although this did credit to the linguistic ability of American patholo-

gists, it tended to cause confusion among legislators involved with the issue of black lung and claims examiners in the U.S. Department of Labor. To address this problem and to attempt to define standards for CWP, the National Institute for Occupational Safety and Health (NIOSH) contracted with the College of American Pathologists in 1977 to produce a set of pathologic standards for CWP. This project was completed by the Pneumoconiosis Committee of the College of American Pathologists in 1979 and was published in the *Archives of Pathology* in July of that year.[43] In their report the committee defined the essential lesion for the pathological diagnosis of CWP as "a focal collection of coal dust pigment-laden macrophages at the division of respiratory bronchioles which may exist within alveoli and extend into the peribronchiolar interstitium with associated reticulin deposits and focal emphysema". These criteria were considered the most appropriate because the coal macule and focal emphysema are found in the lungs of coal workers exposed to different types of coal mined under widely divergent conditions in the United States,[43, 44] Great Britain,[45, 46] Australia,[47] and South Africa.[48]

Many other lesions are seen in the lungs of coal workers, and some of these are undoubtedly related to coal mine dust exposure. Within this latter group should be placed the nodular lesions of coal workers, progressive massive fibrosis (PMF), and Caplan's syndrome. The relationship of bronchitis, nonfocal emphysema, pulmonary vascular disorders, and lung cancer to coal mine dust exposure is less clearly understood and is the subject of continuing research and controversy. In contrast to the basic lesion outlined above, the incidence of all these other conditions varies greatly from country to country, from mine to mine, and according to personal habits and genetic factors. A classification of the pulmonary lesions of coal workers is shown in Table 1. Clinically and radiologically, CWP is classified into simple and complicated forms based on the size of the pulmonary opacities. In general, simple CWP corresponds with the macular and nodular lesions of coal workers, and complicated CWP corresponds with PMF and the lesions of Caplan's syndrome.

Macular CWP

The pleural surfaces of a coal worker's lungs show a marbled distribution of bluish-black pigment which is similar in appearance but more extensive than that seen in urban dwellers. The distribution of the pigment corresponds to the lymphatic channels in the junction sites of secondary lobular septa and the pleura. Pleural thickening is not usually pronounced unless nodular lesions or PMF are also present. On cut section, a suitably inflated lung will show numerous uniformly distributed areas of black pigmentation (Fig. 2). These are the coal macules, which may number up to five in each secondary lobule. Characteristically, the density of the lesions is greatest in the upper parts of the upper and lower lobes. The macules range in size from 1 to 5 mm in diameter and may be rounded, irregular, or stellate in shape. A zone of enlarged air spaces 1 to 2 mm in extent is usually, but not always, seen around the macule (Fig. 3). This constitutes the focal emphysema. The macules are not palpable, a feature which distinguishes them from the

TABLE 1. Classification of the Pulmonary Lesions of Coal Workers

1. Macules
2. Nodules
3. Progressive massive fibrosis (PMF)
4. Rheumatoid pneumoconiosis (Caplan's lesion)
5. Interstitial fibrosis and honeycomb lung
6. Bronchitis
7. Emphysema
8. Pulmonary vascular disorders
9. Bronchial neoplasms (?)

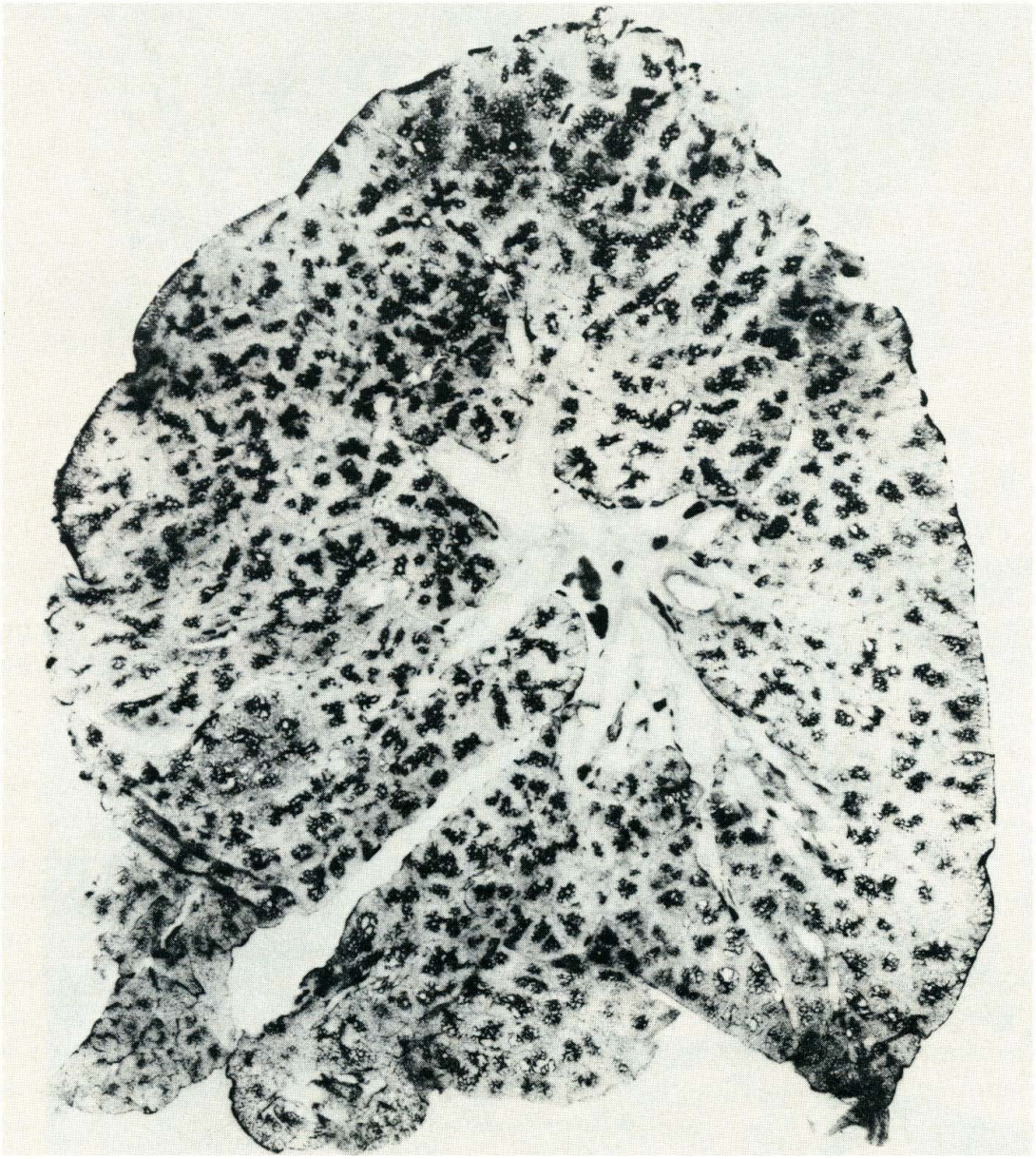


FIG. 2. A 48-year-old Caucasian coal miner worked underground for 18 years at various jobs; 30 pack-year smoking history. Died of bronchoalveolar cell carcinoma (not shown). Whole lung section shows numerous macular lesions with characteristic lobular distribution. There is minimal focal emphysema.

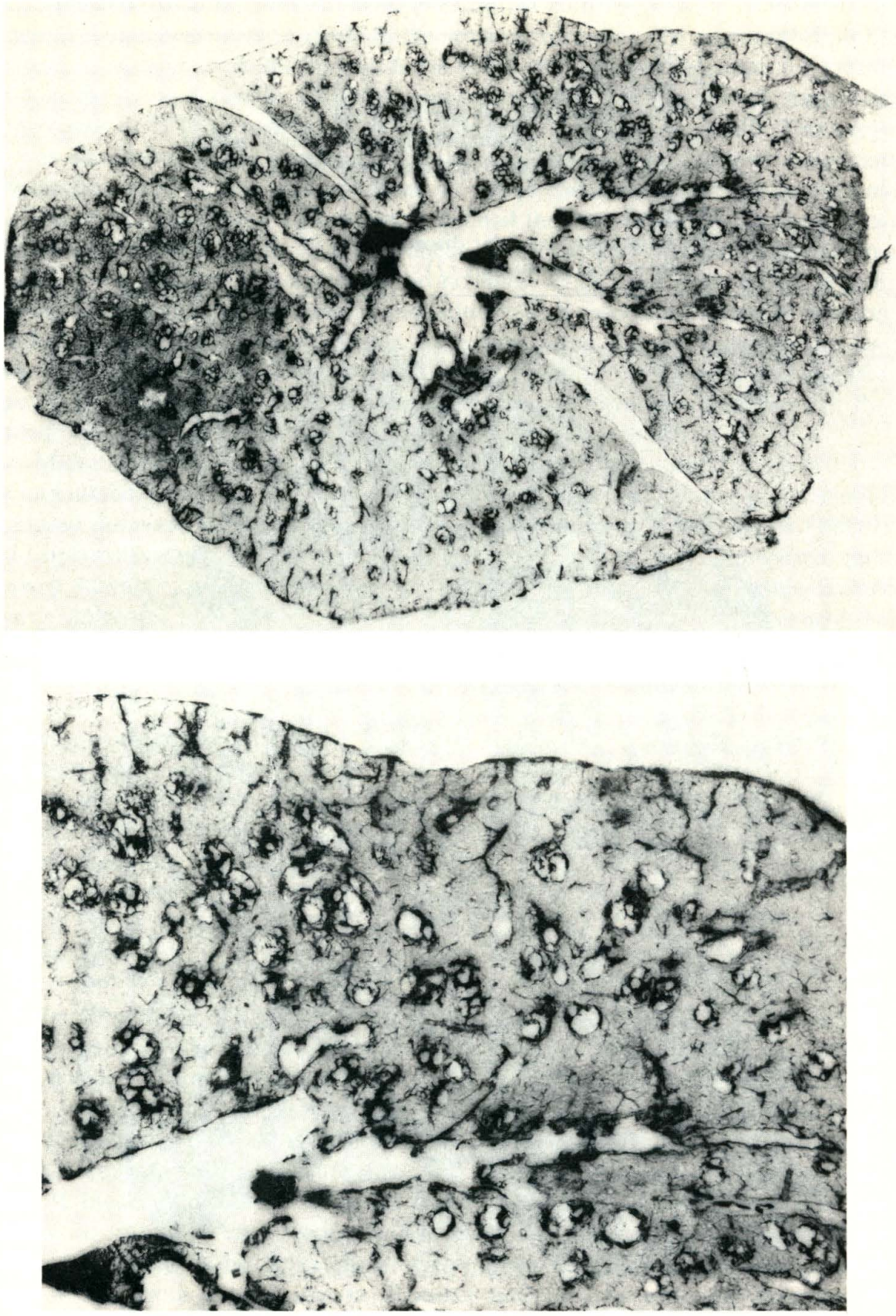


FIG. 3. A 78-year-old Caucasian coal miner worked 48 years underground; smoked a pipe. **Top.** Whole lung section shows sparse macules with focal emphysema. **Bottom.** Close-up of coal macules and focal emphysema. (Continued)

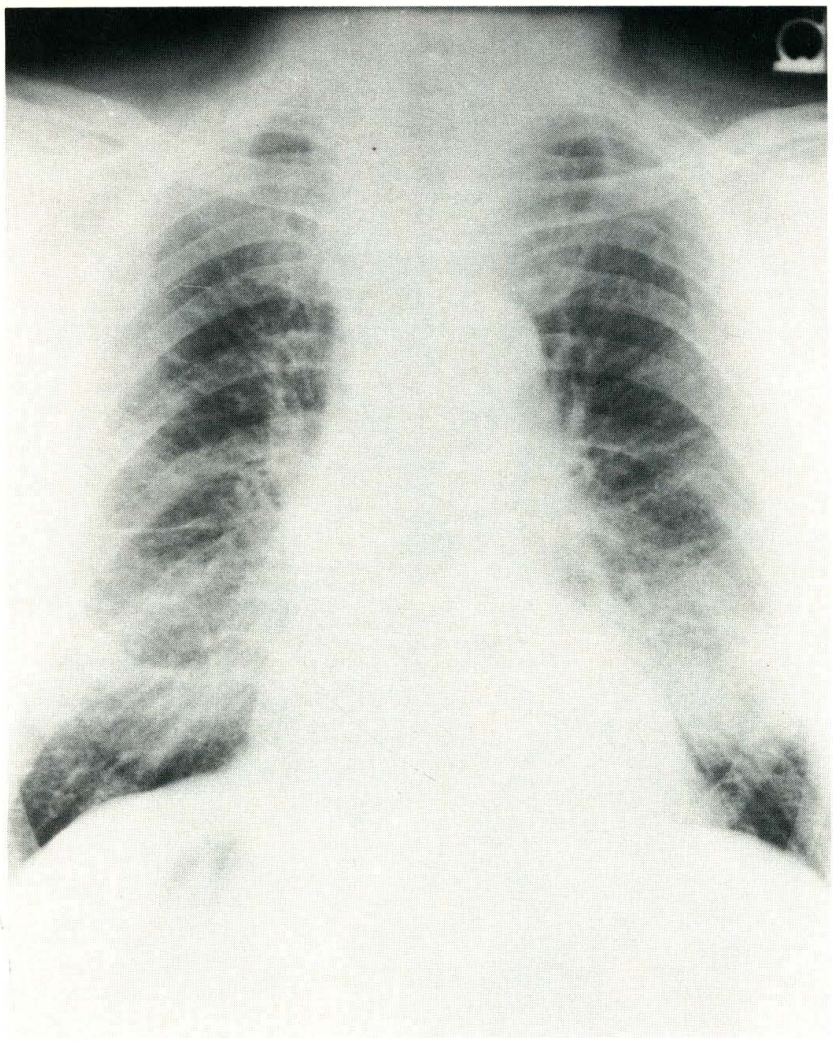


FIG. 3. (cont.) Chest roentgenogram shows rounded opacities category 2q and irregular opacities category 1t.

nodular forms of CWP. The lymph nodes in the peribronchial, hilar, and paraaortic regions are usually enlarged, soft, and densely pigmented in coal workers.

Microscopically, the macule is composed of coal-dust–laden macrophages which surround the first-, second-, and third-order respiratory bronchioles and extend into and fill the adjacent alveoli (Fig. 4). The majority of these lie external to the muscle coat of the respiratory bronchioles. A fine network of reticulin runs between the closely packed macrophages, together with a variable amount of collagen. The latter increases with age and duration of exposure.[44] In the lungs of active or recently retired miners, considerable numbers of pigmented macrophages may be seen in the alveoli that arise from the respiratory bronchioles. In some cases the alveoli may be completely filled with macrophages, and the alveolar walls appear partially collapsed around them.[49] Coal-dust-containing macrophages are also seen in the adventitia of the small pulmonary arteries.

The focal emphysema is most marked at the level of the second-order respiratory bronchiole, which corresponds with the site of maximum dust deposition.

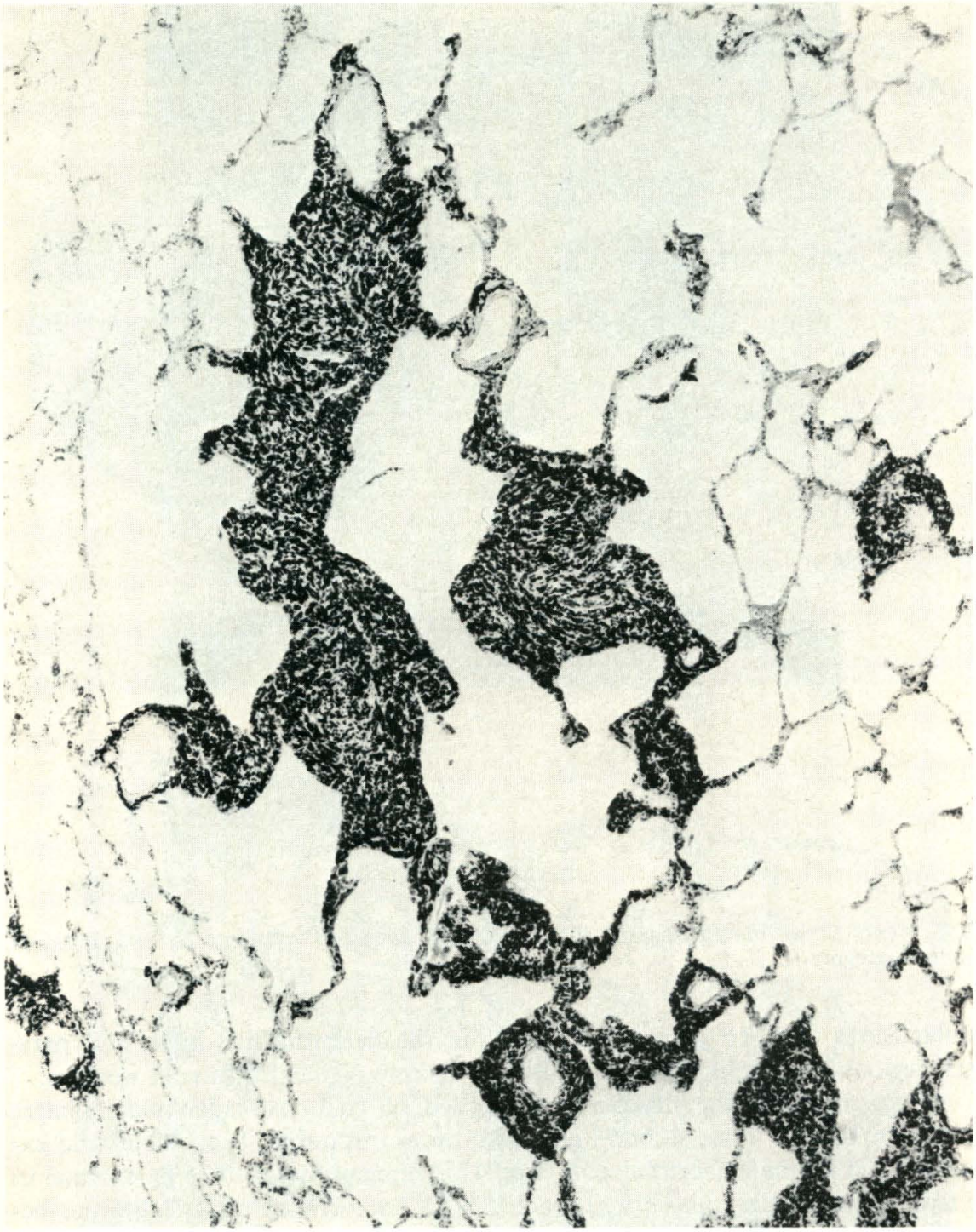


FIG. 4. Coal macule showing relationship to respiratory bronchiole. The lesion is composed of pigmented macrophages in a reticulin stroma. H&E. ×98.

In this region the walls of the respiratory bronchioles show atrophy of the smooth muscle bundles. The alveolar ducts and more distal parts of the acinus are unaffected. Fusion of adjacent dilated respiratory bronchioles presents a complex histologic pattern which may require the use of serial sectioning microscopic techniques for clarification.[45] Initially the emphysema is distensive rather than destructive in nature and is probably of limited clinical significance.[50] In some cases,

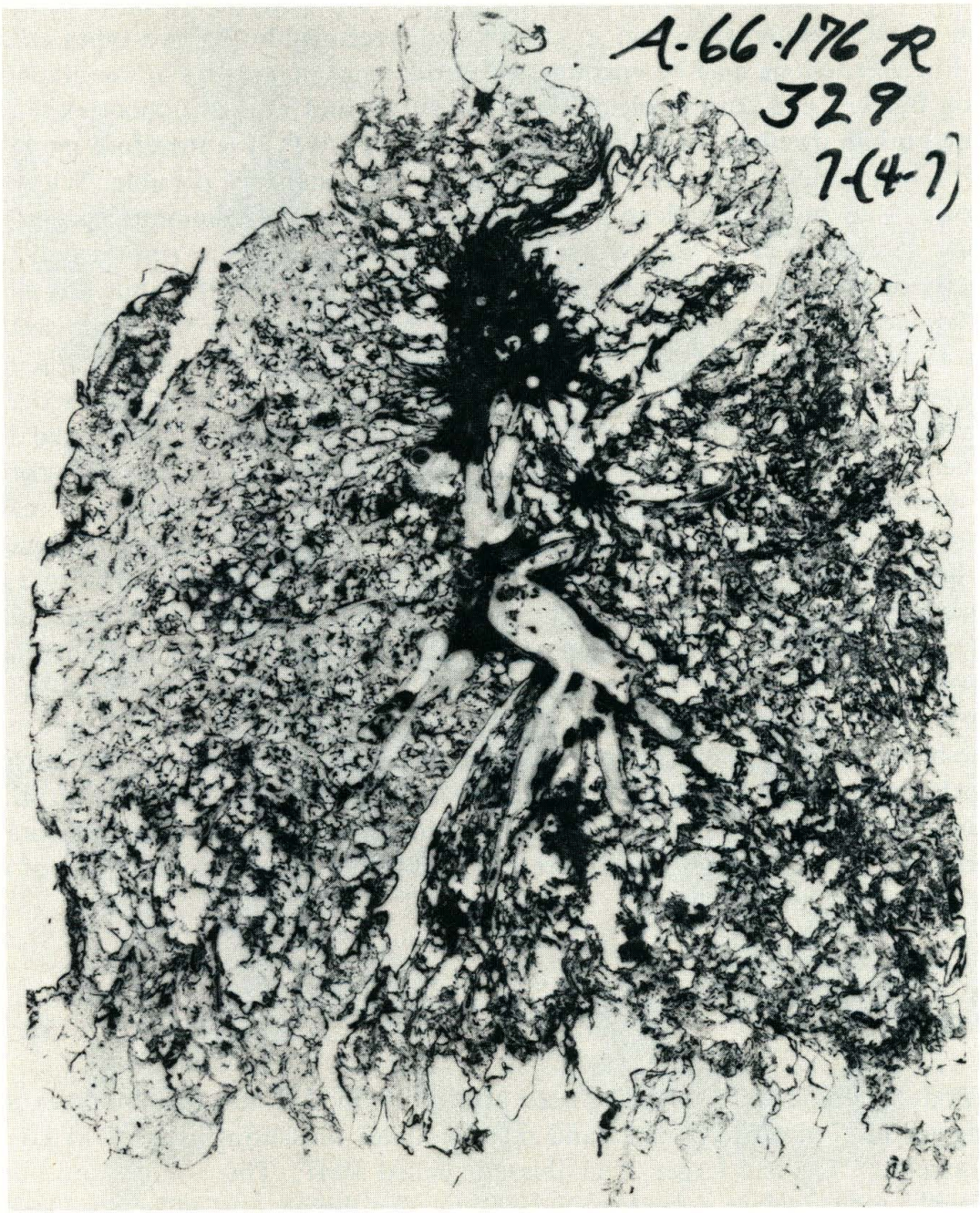


FIG. 5. A 77-year-old miner, worked 24 years underground as loader, no smoking history. Whole lung section shows progressive massive fibrosis against a background of macular and nodular disease. There is an apparent progression of the focal emphysema (seen at left) to emphysema of panacinar type (at right). Severe scar and bullous emphysema are also present.

destructive changes supervene, and the emphysema becomes confluent (Fig. 5). Focal emphysema and centriacinar emphysema not associated with dust involve the same anatomic location and may be difficult to distinguish in the presence of the coal macule. It has been disputed that they represent distinct forms of emphysema.[51] Heppleston believes that the lesions can be distinguished by the presence of respiratory bronchiolar disruption and inflammatory fibrosis in centriacinar emphysema without dust and by their absence in focal emphysema.[30, 50] In prac-

tice it is often difficult to make these distinctions; especially in the more advanced stages of focal emphysema and in cases where presumably the two types coexist.

Macular lesions may be encountered in the lungs of workers in the graphite,[52] carbon black,[53] and carbon electrode [54] industries, and also in nonoccupationally exposed urban dwellers. In making the diagnosis of CWP, it is therefore important that the intracellular pigment be identified as accurately as possible. With light microscopy at high magnification, respirable particles of bituminous coal appear angular in outline (Fig. 6), yellowish-brown in color, and are translucent. Coal particles derived from anthracite coals are also angular in outline but are darker in color and do not transmit light. Coal dust particles seen in the tissue sections range in size from 10 to 0.2 μm (the limits of resolution of the light microscope), and have a mean diameter of approximately 1 μm.[55] The sooty particles derived from combusted fossil fuels and organic material are opaque, black, and have rounded borders. They are frequently aggregated into clumps. Cigarette smokers may also show a diffuse, finely granular, tan pigment in the cytoplasm of macrophages.[18] An electron microscopic study of pulmonary pigment in four coal miners with both simple and complicated CWP [56] showed four types of electron-dense particles which were common to all the lungs: (1) hard, dense, needlelike bodies which were associated with the cytosomes; (2) smooth, angular pieces associated with cytosomes and lying free in the cytoplasm; (3) hard, rectangular "chunks" associated with the cytoplasm; and (4) granular aggregates which were not membrane-bound and appeared to be a composite of the other types. The particles ranged in size from 0.1 to 5 μm but unfortunately could not be positively identified. It would be of value if this work were repeated using x-ray analytic procedures to facilitate identification of the particles and thus relate specific components of coal mine dust to cellular pathology.

Nodular CWP

The nodular lesions of CWP have been arbitrarily divided into micronodules measuring up to 7 mm in diameter and macronodules measuring from 7 to 20 mm in diameter.[43] Lesions larger than this are called PMF. The nodules are almost invariably seen against a background of macular disease and, like macules, are more numerous in the upper parts of the lung (Fig. 7). They are readily palpable and on section appear as irregular black lesions with spiderlike processes that extend out into the surrounding lung parenchyma. They are associated with a variable amount of scar emphysema. They are usually situated in the region of the respiratory bronchioles but may also be seen in the pleura and in the peribronchial connective tissues. Nodules tend to coalesce to produce the lesions of PMF (Figs. 8, 9).

Microscopically, two basic histologic patterns are recognized:

1. Simple dust, macrophage, and reticulin nodules (Fig. 10). Histologically, these lesions are similar to macules. They are distinguished from each other only on the basis of size and palpability.

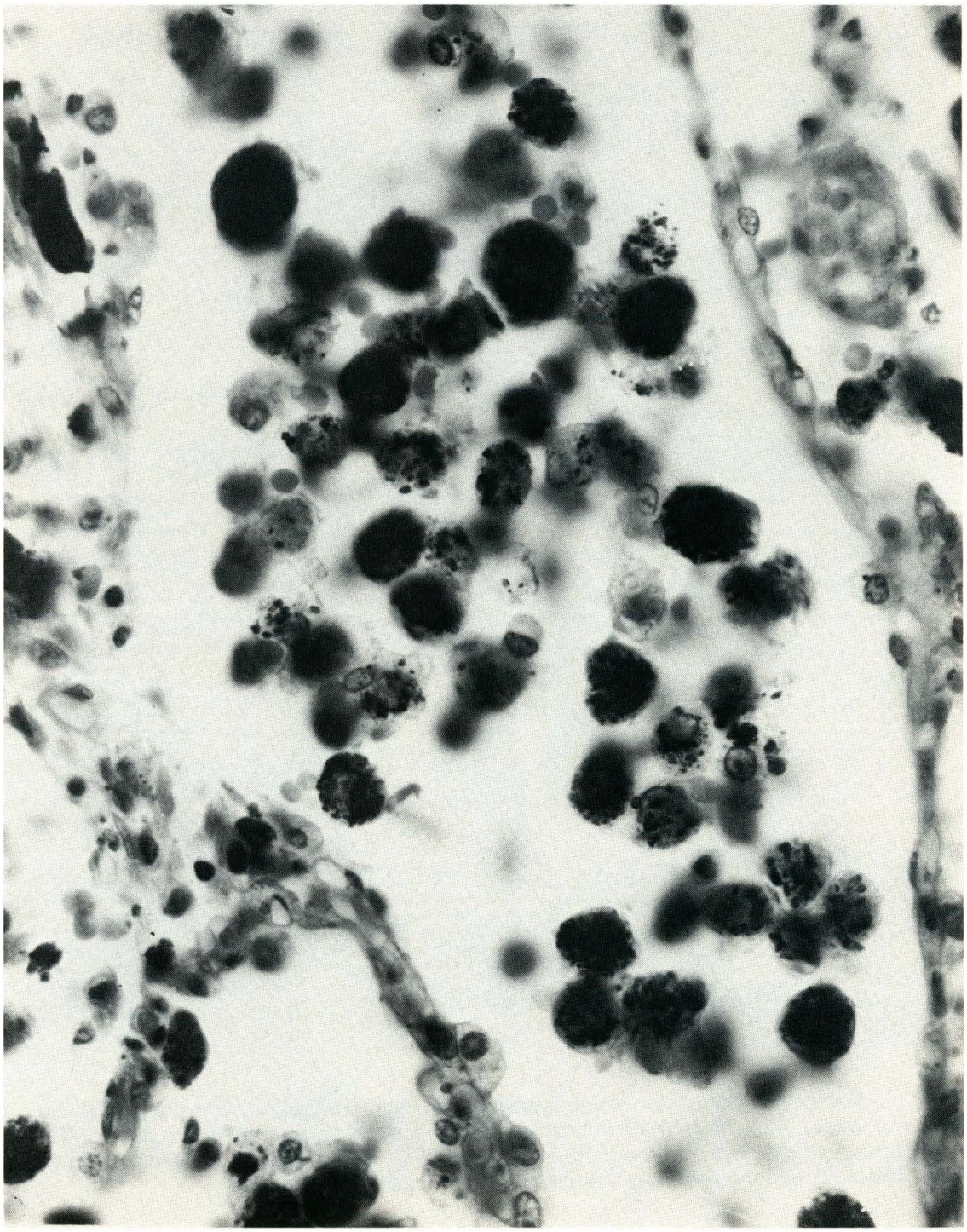


FIG. 6. Alveolar macrophages in alveolus of an active miner. The number of coal particles (bituminous) in each cell varies greatly. The particles range in size from 0.2 to 3 μm and have angular borders. H&E. $\times$585.

2. Mixed nodules. These are the most common type and are composed of pigmented macrophages in a dense network of reticulin and collagen (Fig. 11). They differ histologically from the macule only with respect to the amount of collagen present. Mixed nodules are distinguished from silicotic nodules by increased reticulin content and the haphazard arrangement of the collagen fibers

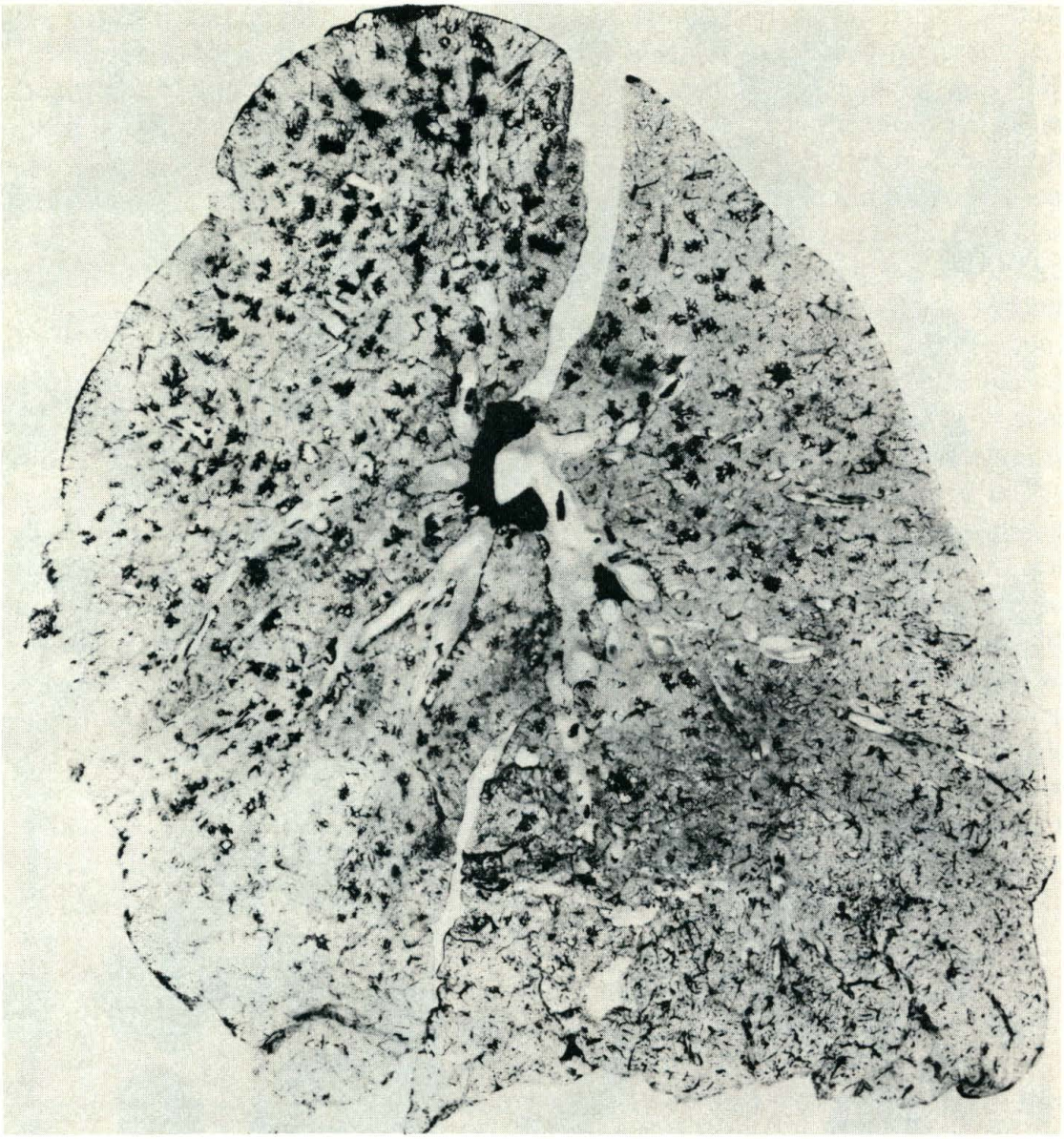


FIG. 7. A 66-year-old Caucasian miner, worked 42 years underground at a variety of jobs including loader, shot firer, and trackman; smoked a pack of cigarettes per day for 45 years. Whole lung section shows micronodules and macules with minimal focal and scar emphysema. The dust lesions are more numerous in the upper zone.

in the former and decreased reticulin and concentric whorling of collagen fibers in the latter. The mixed nodules are often referred to as "anthraco-silicosis," [33] a term best avoided until such time as their relationship to silica is better understood.

The blood vessels within and adjacent to the nodules described under (1) and (2) frequently show marked obliterative vasculitis. Infarcts may occur in the center of even quite small lesions with the formation of cavities containing free pigment (Fig. 12). These vascular changes are indistinguishable from those seen

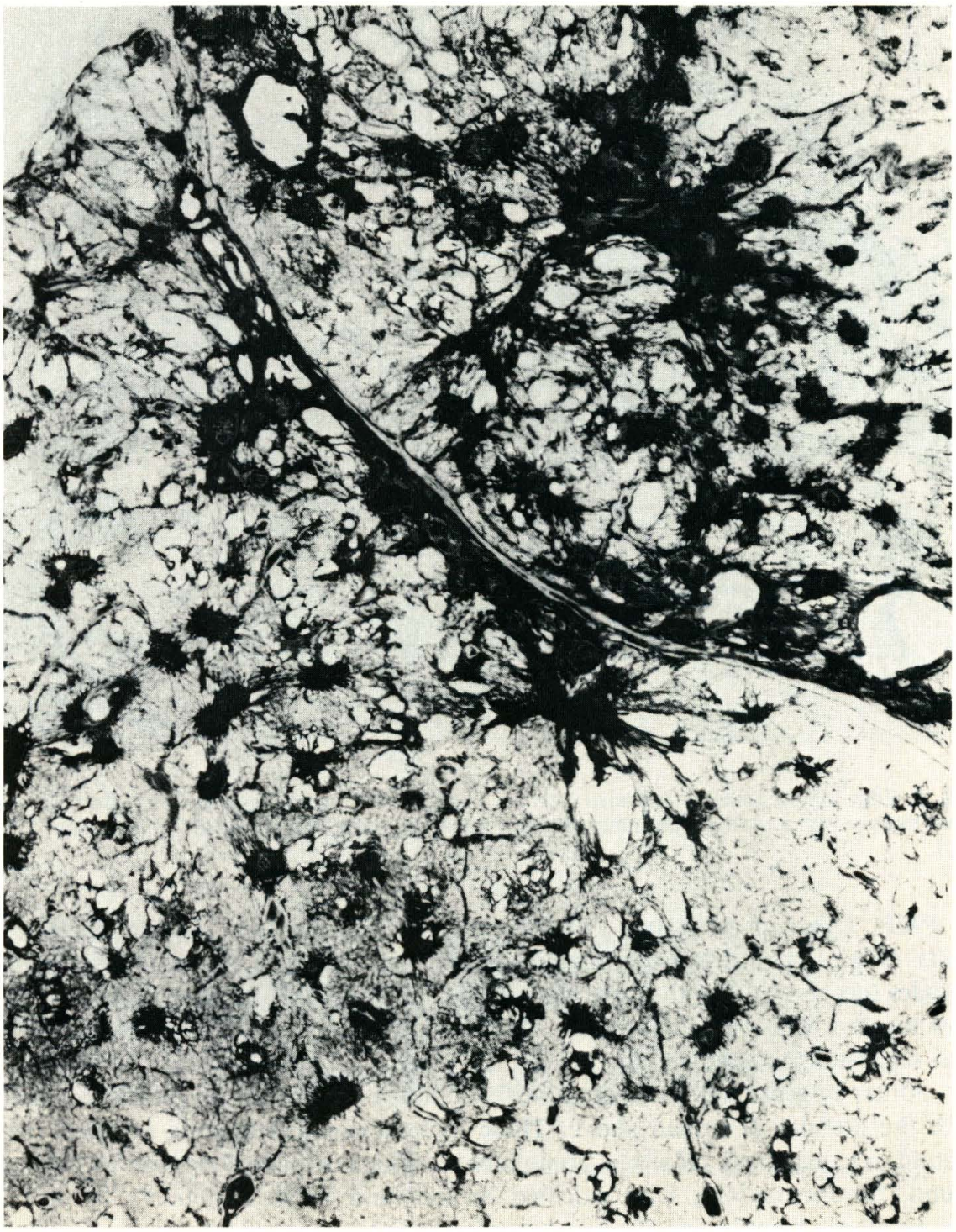


FIG. 8. An 80-year-old Caucasian coal miner, worked 22 years underground; smoked a pack of cigarettes per day. Close-up of whole lung section shows micro- and macronodules, which are becoming confluent in the region of the lobar fissure. There is a moderate degree of scar emphysema. Macules with focal emphysema are seen at bottom.

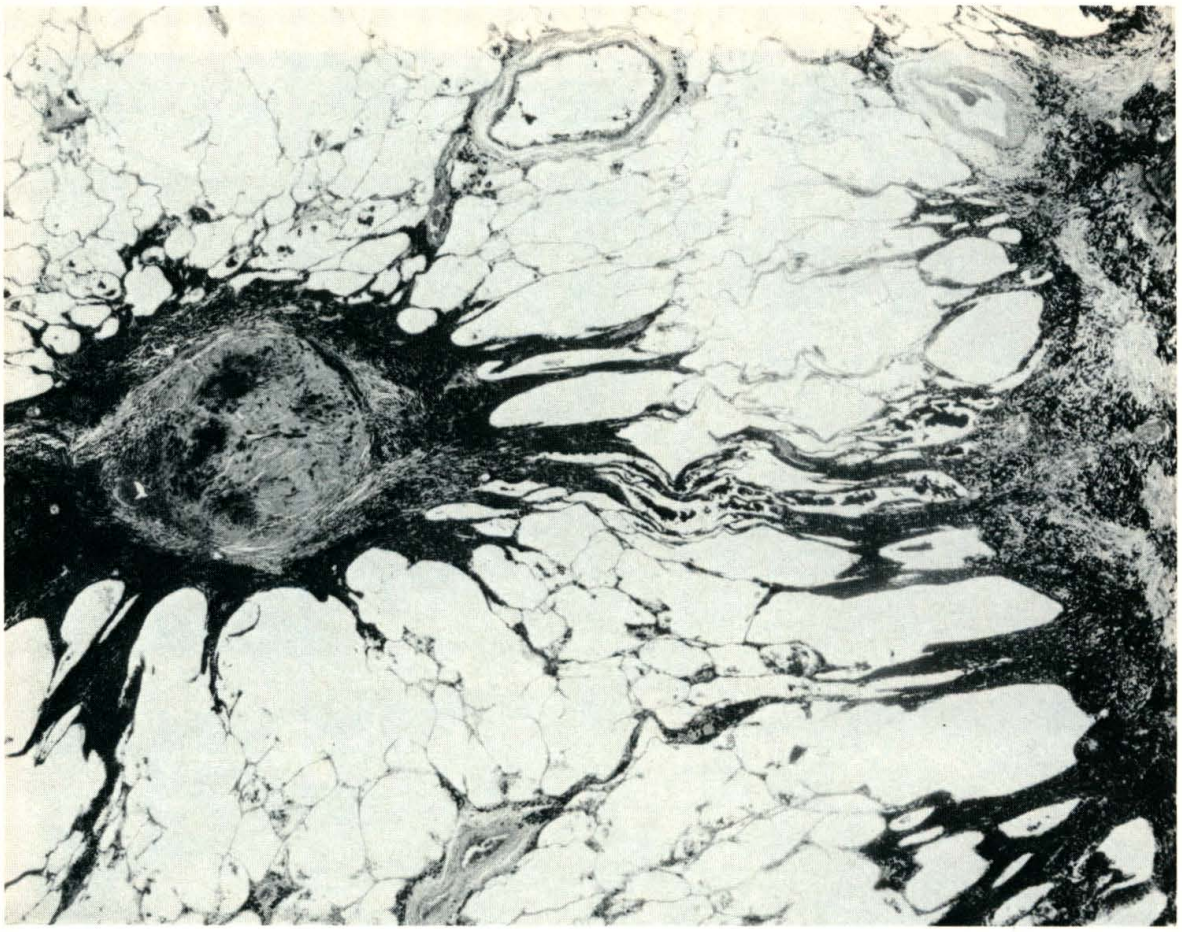


FIG. 9. Edge of progressive massive fibrosis (right) with mixed nodule (left). Both lesions have deeply pigmented serpiginous borders together with marked scar emphysema. H&E. ×16.

in PMF. Other degenerative changes seen in coal nodules include cholesterol clefts (Fig. 13) and less commonly calcification. Electron microscopy of mixed nodules has shown that they are composed of collagen fibers, fibroblasts, and coal dust together with an unidentifiable amorphous material in the center of the nodule that separates the collagen fibers.[57]

Other nodular lesions in coal workers' lungs may cause diagnostic confusion with the nodules described above. These include classical silicotic nodules, rheumatoid nodules, and infective granulomata. The last-named appear as distinct, round, fibrotic nodules with calcified centers and varying amounts of dust in the periphery (similar to chronic histoplasmosis). The various types of nodules described above are not exclusive entities; it is relatively common to find individual nodules that show the features of more than one type and also to find two or more distinct types of lesions in the same lung (Fig. 14).

PATHOGENESIS OF CWP

The fact that the coal macule with focal emphysema occurs against a background of exposure to a wide variety of coals would point to the existence of a common factor for the formation of the basic lesion. The most likely agent is the relatively

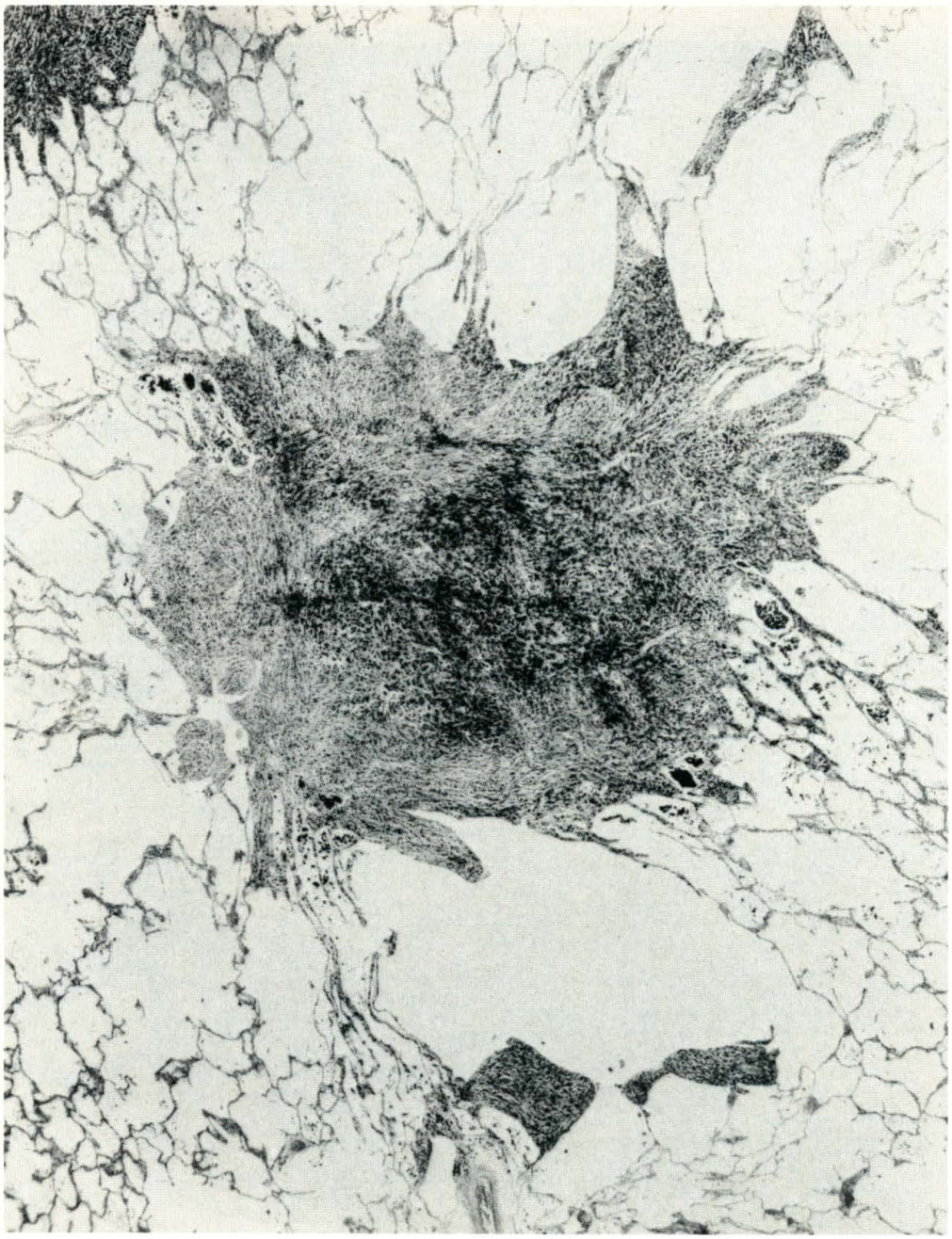


FIG. 10. Micronodule, low-power view. The lesion is composed of uniformly dispersed dust in a predominantly reticulin stroma. H&E. ×18. (Continued)

inert carboniferous component of the coal. This concept is supported by the observation that classical CWP occurs in coal trimmers who work above ground and are exposed to negligible amounts of rock dust.[58] Similar lesions are also seen in workers exposed to pure carbon.[53, 54]

A further factor of major importance in the pathogenesis of CWP is the relationship of dust exposure to clearance. Epidemiological studies on large populations of working miners have shown that progression of simple CWP is determined by cumulative dust exposure,[11, 59] and that levels of coal mine dust below 2 mg/m^3 theoretically result in zero incidence of disease.[11] The implication of these stud-

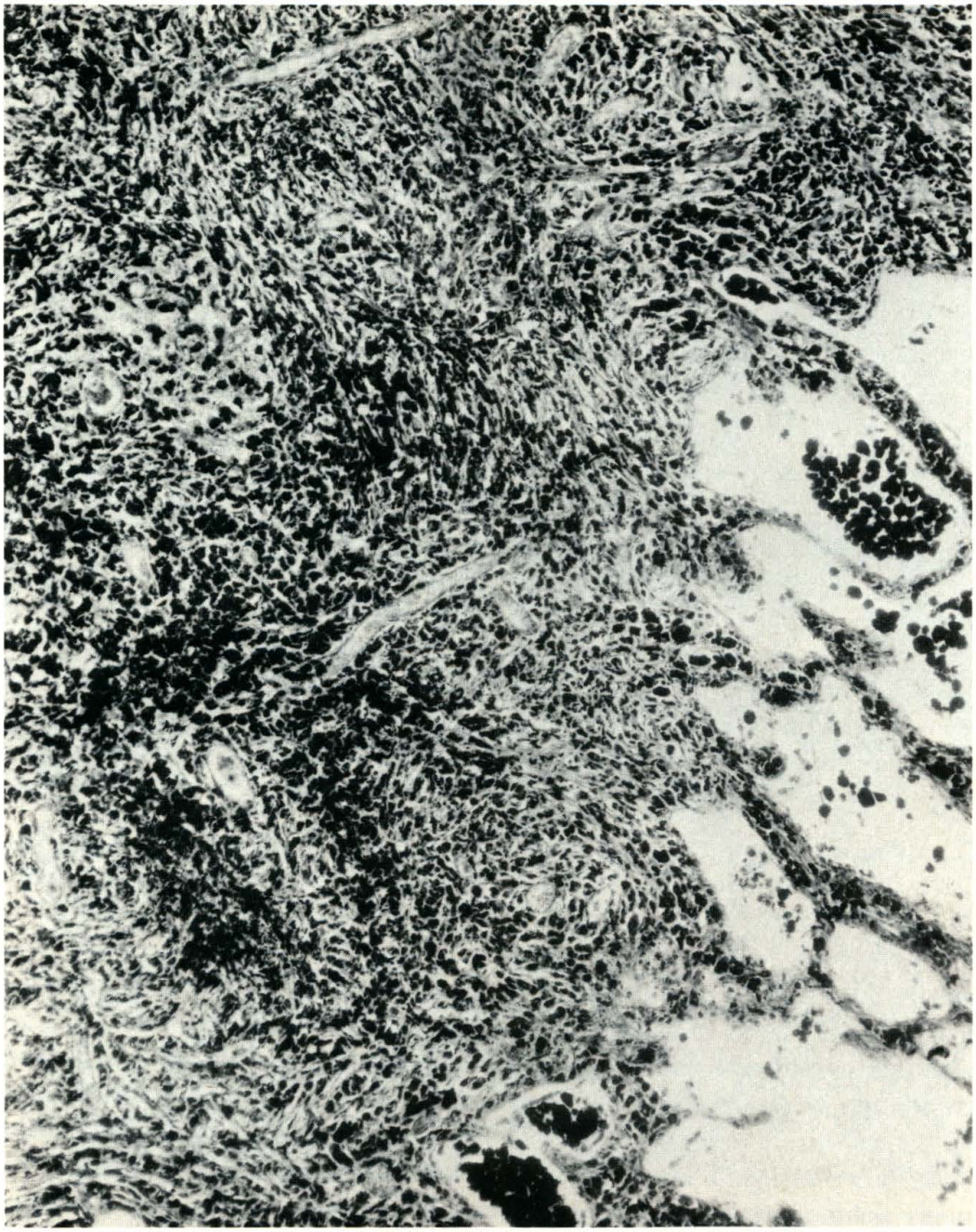


FIG. 10. (cont.) High-power view. Dust-containing macrophages lie in a reticulin stroma. Numerous blood vessels are present. Collections of pigmented macrophages in the adjacent alveoli suggest recent exposure. H&E. ×180.

ies is that simple CWP results if the ability of the lung to clear dust is overwhelmed. The site of formation of the macule would point to an anatomic weak point in the clearance pathway. Dust cleared by both the interstitial lymphatics and by the alveolar macrophages passes through the narrow region of the respiratory bronchiole. The surface area of the airway at this point may be 1/500th of that of the lobule at the level of the alveolus.[18] Moreover, the surface of the respiratory bronchioles is discontinuous due to the alveoli which arise from them and lacks the ciliated epithelium of the more proximal airways.

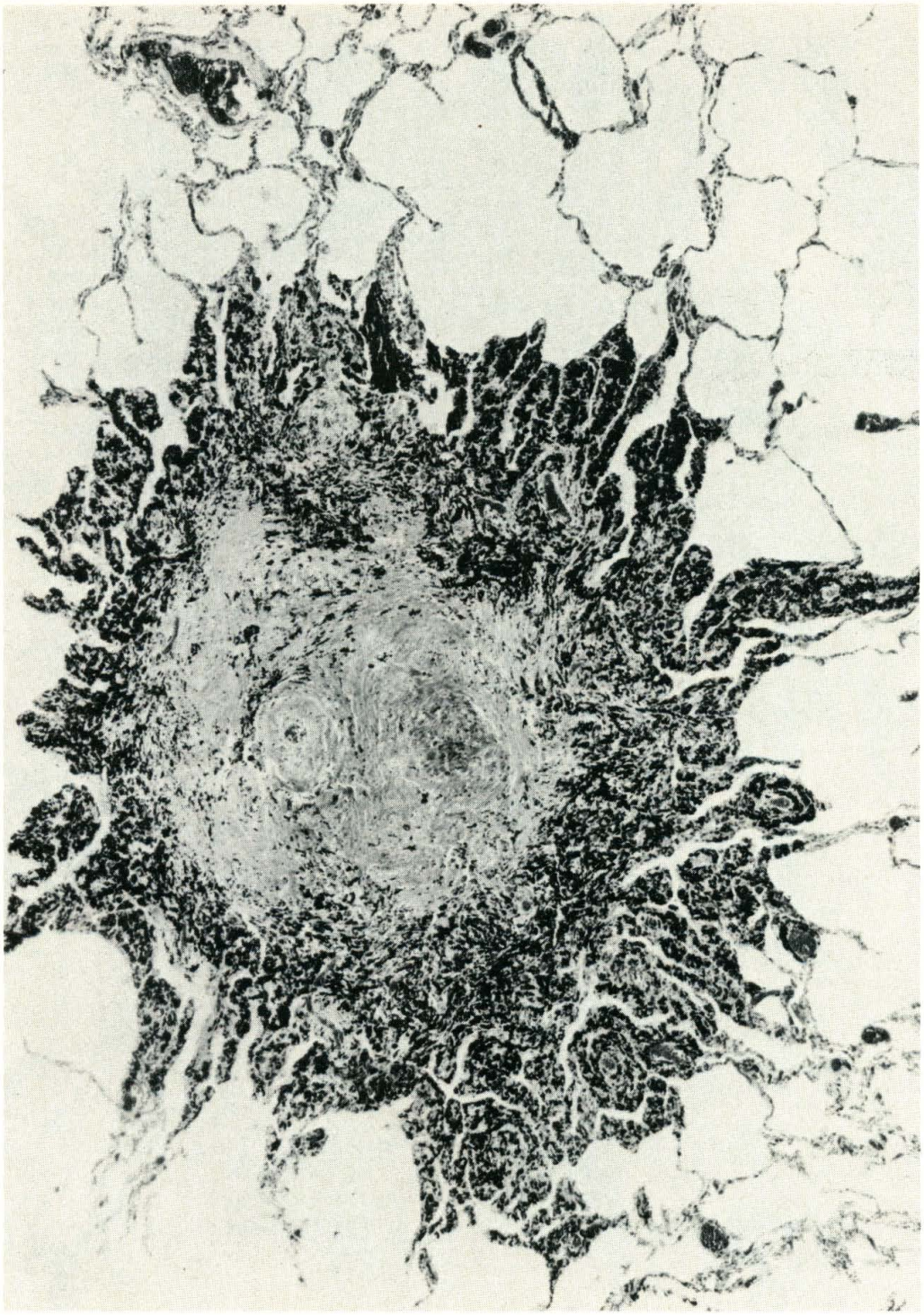


FIG. 11. Micronodule. The center of the lesion is composed of hyalinized, irregularly arranged collagen bundles. The remains of a small obliterated artery are discernible within the central collagen. H&E. ×98.

In an active miner, masses of pigmented macrophages accumulate in the alveoli adjacent to respiratory bronchioles. The affected alveoli appear to collapse around the macrophages. It has been suggested that the macule grows by the incorporation of these consolidated alveoli into the wall of the respiratory bronchiole.[30, 49] The cellular events that follow the deposition of dust are not well

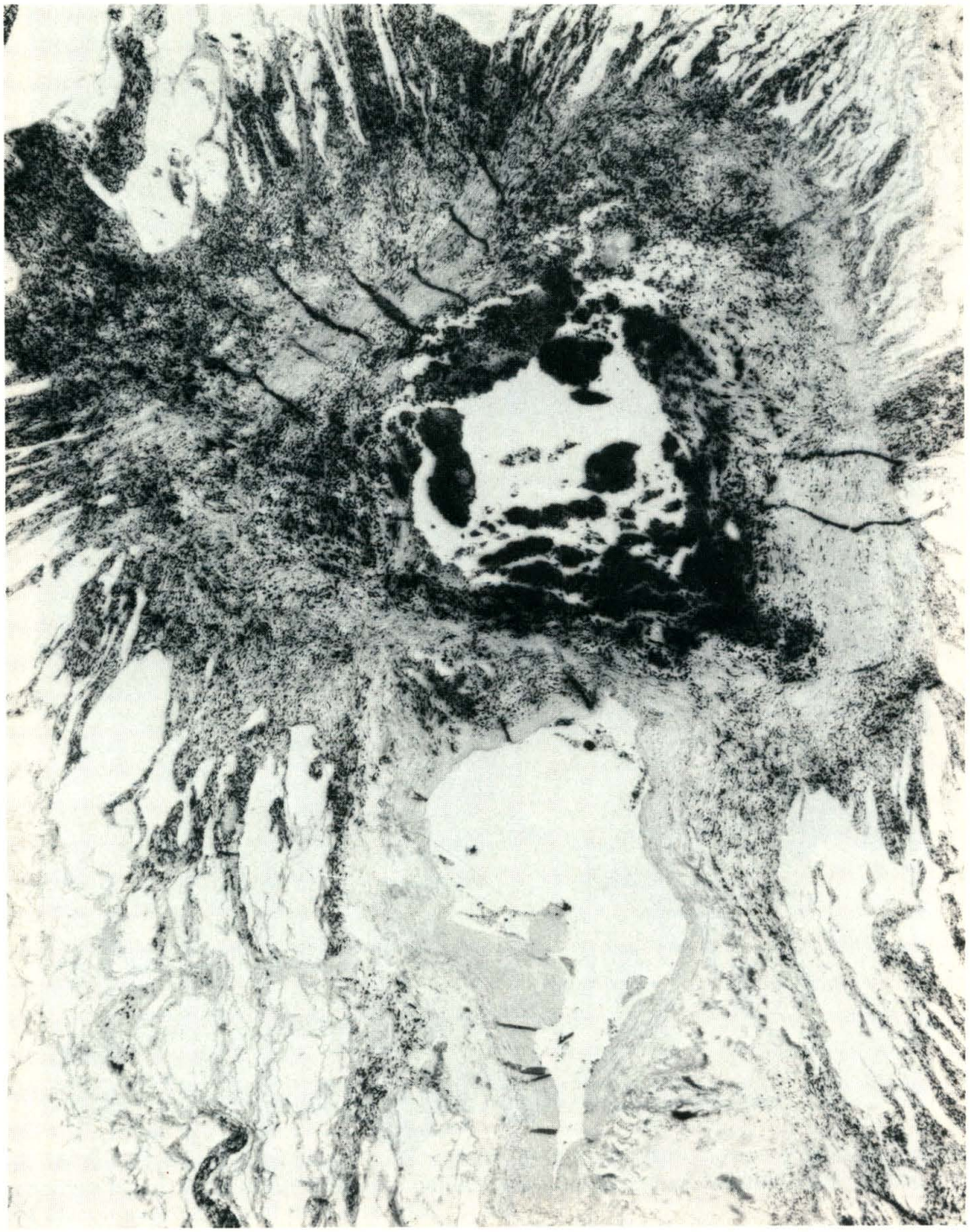


FIG. 12. Mixed nodule composed of dust, reticulin, and haphazardly arranged collagen. Note the central cavitation and involvement of the pulmonary artery in the fibrotic process. These features are also seen in progressive massive fibrosis. H&E. ×20.

understood. Experimentally, so-called inert substances such as pure carbon are capable of stimulating the migration of mononuclear cells from the pulmonary vessels and causing increased mitotic activity in the interstitial macrophage population.[60] There is also evidence that activated macrophages produce factors that stimulate fibroblasts to produce collagen.[61] Coal dust is biologically relatively inert,

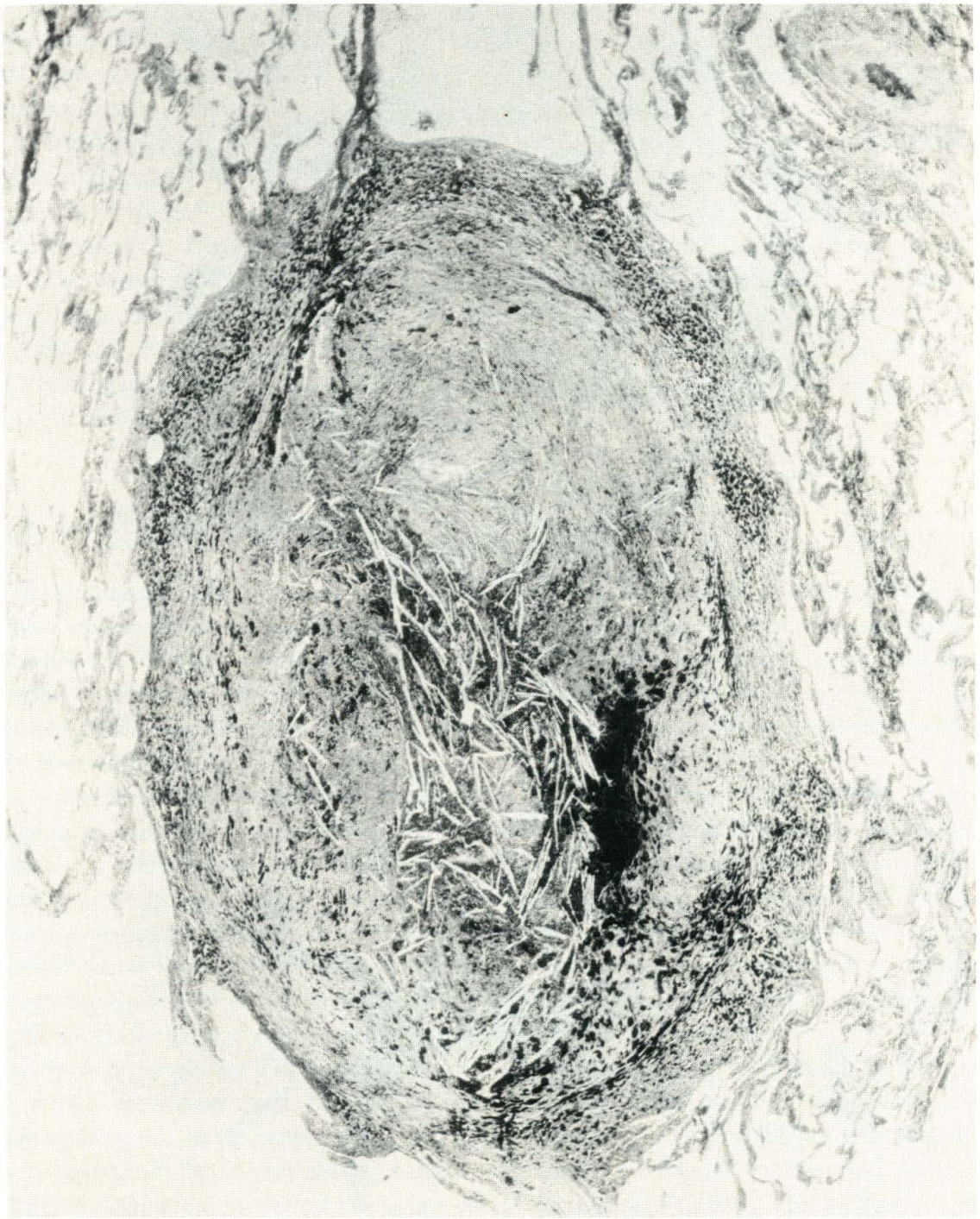


FIG. 13. Nodule showing central necrosis and cholesterol clefts. These two features are also seen in Caplan's lesions and infective granulomata. Differentiation is made on the presence or absence of features such as dust rings and fibroblast palisading and by special stains. H&E. ×20.

and the mild reticulin reaction in the coal macule could result from the above mechanisms.[62] The formation of collagenized nodular lesions probably results from the mineral component of the dust, though this is not established.

The pathogenesis of the focal emphysema is less clearly understood. The lesion, according to Heppleston,[50] is due to a combination of muscular atrophy of

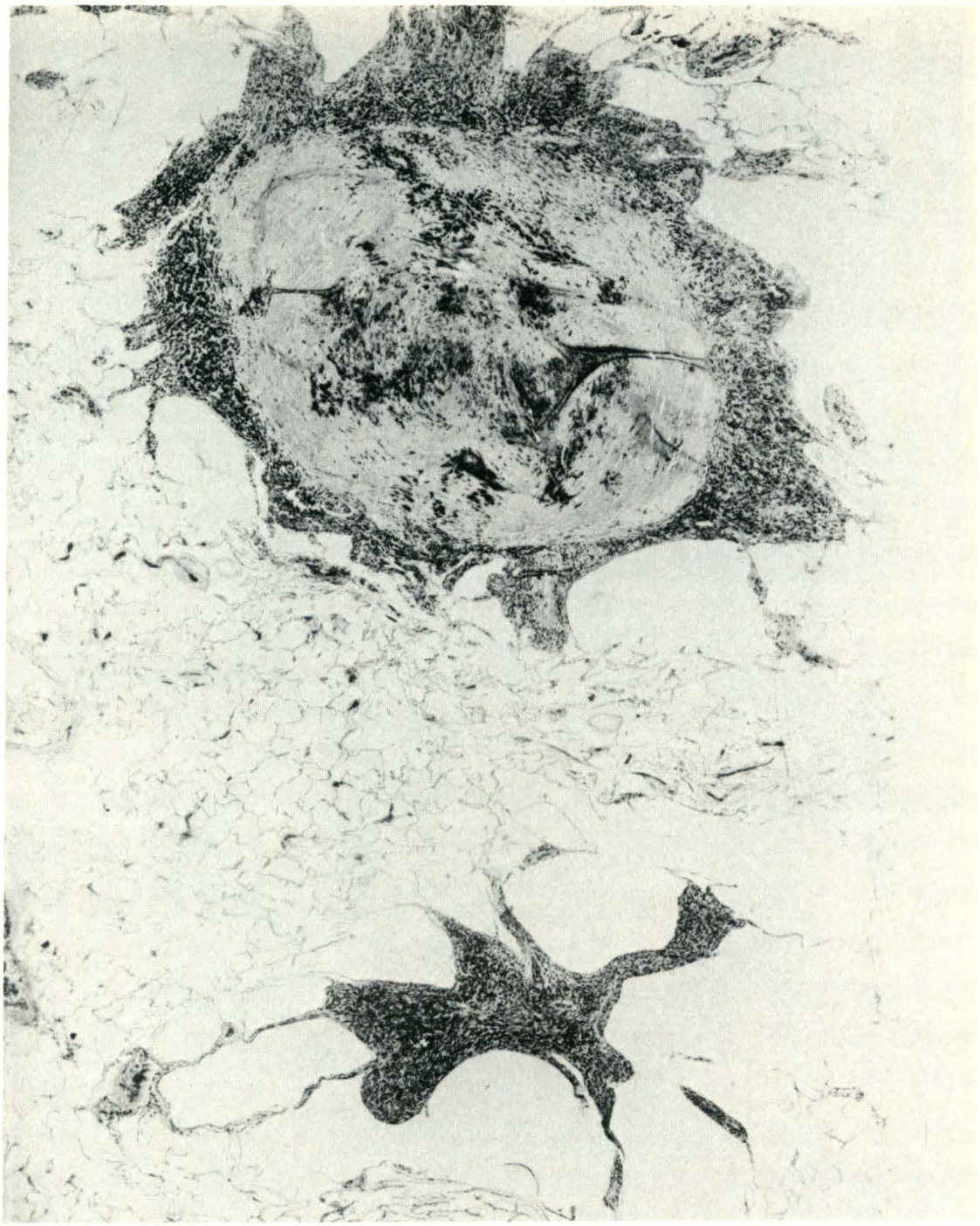


FIG. 14. Coal macule with focal emphysema adjacent to a mixed nodule. H&E. ×20.

the respiratory bronchiole and altered mechanical forces resulting from consolidation of adjacent alveoli. Thus the inspiratory force normally expended on the alveoli is transmitted directly to the respiratory bronchiole, which consequently dilates. This purely mechanical view of the lesion does not adequately explain the destructive element to the focal emphysema. The role of the proteolytic enzymes collagenase and elastase, released from stimulated macrophages, deserves more attention in this regard.[63] Attempts to reproduce the lesions of CWP in animals have

for the most part been disappointing. Macular lesions similar to those seen in man have been produced in guinea pigs [64] and vervet monkeys [48] exposed to coal mine dust and appear to arise by a similar mechanism. Focal emphysema has not been produced experimentally.

Epidemiologic studies have shown that the prevalence of CWP and mortality from lung disease in coal workers varies markedly from mine to mine and from region to region.[8, 13, 15, 62] To some extent these variations reflect differences in criteria used for the selection and diagnosis of cases. However, they also emphasize the importance of local factors in the pathogenesis of CWP. Some of these factors have been identified; others undoubtedly remain to be discovered. Known factors include the rank of coal and its elemental and mineral composition, the nature of the adjacent rock strata, the methods employed in the recovery of the coal, and the specific occupation of the miner.

Coal Rank

Several studies have shown a relationship between the rank of coal and CWP; the higher the rank, the greater the prevalence of both the simple and the complicated forms.[6, 8, 65, 66] The reason for this association is not clear. Analysis of data from studies conducted in English and Welsh coal fields has shown that miners of higher-ranked coals were exposed to a greater mass of respirable dust than were miners of lower-ranked coals.[11]

The increased prevalence of CWP in the Pennsylvania [6] and South Ruhr [13] high-rank anthracite coal fields may be related to quartz exposure. Pulmonary lesions in Pennsylvanian anthracite coal workers contained more silica crystals than lesions in bituminous miners.[6] This is surprising in view of the fact that anthracite usually contains less mineral matter and free silica than lower-ranked coals.[13] However, anthracite coal is usually formed in association with undulating strata composed of sandstones and sandy shales. Thus the mining of the high-rank coals is likely to generate greater quantities of quartz dust.

The pathogenicity of high-rank coals cannot be entirely explained on the basis of either increased dust burden or increased silica exposure.[59] Experimentally, high-rank coals have been shown to be more cytotoxic to guinea pig macrophages than low-rank coals containing similar amounts of mineral matter and quartz.[15] Rank of coal also appears to have an effect on clearance rates. Heppleston et al.[67] have shown experimentally that dust from a high-rank coal mine was cleared at a slower rate from the lungs of rats than was an equivalent amount of dust from a low-rank coal mine. The basis for these differences in biologic reactivity of high- and low-rank coals is not known.

Silica

The relationship of quartz to the development of CWP has received considerable attention and remains a controversial subject. The existence of classical CWP in coal trimmers, who are exposed to negligible rock dust, is evidence that CWP

occurs independently of silica exposure.[58] The important question is therefore not whether silica is necessary for the development of CWP, but to what extent it contributes to the progression of the disease. It is evident from a number of epidemiologic studies that silica exposure is a variable of relatively low significance.[13, 15, 59, 68] Several attempts have been made to correlate the quartz content of the lungs at autopsy to the severity of the pneumoconiosis.[68-70] Nagelschmidt [71] has shown that the severity of CWP at autopsy is related more to the total dust and total mineral content of the dust than to the concentration of quartz. The mean free silica content in the lung dust was 2.2 percent; moreover, typical silicotic nodules were not seen unless the concentration of silica in the dust exceeded 18 percent. These findings are in keeping with the epidemiologic studies referred to above. Two autopsy studies have shown a slight but positive correlation between the quartz content of the lung and the degree of pneumoconiosis. Sweet et al.[69] analyzed the lungs of miners who had worked in southern West Virginia and showed that free silica concentration in the lung dust ranged from 2.51 percent in miners with no evidence of pneumoconiosis to 3.67 percent in miners with PMF. They also showed a direct correlation between total lung dust and severity of the CWP. Chemical and pathologic analysis of 74 lungs from British coal workers showed those with soft-dust macules had the least total dust, coal dust, and noncoal minerals (including quartz), whereas the cases with nodular CWP or PMF had the most.[70] Comparisons with the exposure data indicated a preferential retention of noncoal minerals, especially quartz, in the cases with the more severe lesions. The role of quartz in the development of fibrotic lesions in CWP has been studied experimentally in rats exposed to coal dust enriched with varying amounts of quartz.[72, 73] These studies have shown a mitigating effect of coal dust on quartz fibrogenesis, which is due to nonquartz silicates and other minerals in the coal. The reaction depends on close physical contact between the mineral and the quartz.[74] The ability of coal dust to reduce quartz fibrogenesis is considerable; Rhesus monkeys exposed to coal dust containing 40 percent quartz failed to produce classic silicotic lesions.[34] The phenomenon has been observed in miners. An epidemiologic survey has shown that exposure to high levels of clay minerals appears to reverse the hazard associated with increasing quartz exposure.[68] Semiquantitative x-ray analytic studies of the different types of pulmonary lesions in coal workers also support this concept.[75]

Nonquartz Minerals

The role of nonquartz minerals and metals in coal has received less attention. The fibrogenicity of three common silicates in coal—kaolin, muscovite, and illite—was shown experimentally to be greater than coal alone but considerably less than quartz.[16] A conclusion drawn from this study was that even though these minerals are capable of reducing the toxicity of quartz, they should be evaluated in the assessment of mine dust toxicity. Another common mineral in coal, hematite, like the silicates, is capable of inhibiting quartz fibrogenesis,[76, 77] but unlike the silicates appears to be nonfibrogenic.[78] The role played by iron and its compounds in

the pathogenesis of CWP has not to our knowledge been examined, though iron is a major component of the mineral content of coal and contributes to the radiologic category of pneumoconiosis.[79, 80] Analysis of coal samples from a Pennsylvania mine associated with a high incidence of CWP showed more Fe, Cu, Ni, Pb, and Zn than coal from a Utah mine with a low incidence of CWP.[81] Aqueous extracts from the Pennsylvania coal were more toxic to mammalian cultured cells.[82] The toxicity correlated with the concentration of nickel in the extract. A dose-response curve using purified nickle chloride in the same assay system, was similar to that produced by the coal extract but did not account for all the toxicity. Sweet et al.[69] have shown that the lungs of bituminous coal workers from southern West Virginia contained more Be, Ti, V, Cu, Ni, Pb, Mg, and Fe than did the lungs from a control population taken from the same area. When the concentrations of these metals were compared to the pathologic grading of CWP, only Be, Mg, and V correlated with increasing severity of lung damage. The data showed no relationship between Cr, Cu, Fe, Mn, Ni, Ti, and Zn and grade of pneumoconiosis. The levels of Be in the cases of PMF were in the same range as those recorded in the lungs of patients with berylliosis,[83] raising the distinct possibility that Be is involved in the conversion of simple CWP to PMF.

The influence of toxic organic compounds and gases in the pathogenesis of CWP is another area of growing research interest. Toxic gases such as SO_2, NO_2, or CO may be generated in the mines from diesel engines, blasting, or welding.[20, 84] The toxicity of these gases may be potentiated by concomitant exposure to inorganic dust.[85]

Infection

Coal mine dust may also affect the ability of the miner to respond effectively to infectious agents. The potentiating effect of coal dust and silica on mycobacterial infections has been well documented and is discussed in detail in the section on PMF. In addition, Hahon [86] has shown that coal dust depresses interferon synthesis in cell monolayers that have been treated with influenza virus, suggesting one mechanism whereby miners might be predisposed to respiratory virus infections.

Genetic Factors

The wide variation in severity of the pulmonary lesions seen in miners of comparable age, smoking, and work histories leads us to believe that genetically determined host factors may be of importance in the pathogenesis of CWP. In an early study, Hutchinson [87] failed to demonstrate a difference in severity of CWP between monozygotic and dizygotic twin brothers. Heise et al.[88] looked for genetic markers of resistance to CWP. They studied the distribution of blood group and histocompatibility (HL-A) antigens in Pennsylvania and West Virginia coal miners. Although they found no association between blood group and category of CWP, which was in accord with a prior study by Higgins et al.,[89] they did show an association between W18 and resistance to PMF. They also demonstrated that HL-

A1 is associated with resistance to the development of both simple and complicated CWP. A subsequent report which extended the population of miners confirmed the latter, but not the former, association.[90] These studies suggest that if there is a link between genotype and resistance to CWP, it is a weak one. There is a need to search for other genetic markers that have better predictive value.

Immunologic Factors

The role of immunologic factors in CWP has been studied in coal workers and in experimental animals. The incidence of circulating rheumatoid factor (RF) and antinuclear antibody (ANA) has been determined in miners in both the United States and in Great Britain. Soutar et al.[91] studied 109 British miners and showed a positive correlation between ANA antibody titers and category of pneumoconiosis. A similar, but less striking, trend was seen with RF. Lippmann et al.[92] also found an association between ANA and category of pneumoconiosis in 207 Appalachian miners but no increase in incidence of the RF. Antilung antibodies and elevated levels of serum and salivary IgA have been demonstrated in the sera and saliva of Appalachian coal workers.[93] Mice also develop lung reactive antibodies and increased levels of serum IgA when exposed to coal dust by inhalation.[94] The role of these immunologic changes in the pathogenesis of CWP is not known. The relationship of immunologic factors to PMF and Caplan's syndrome is discussed in detail in the sections relating to these conditions.

Smoking

It is not possible to complete a discussion on the pathogenesis of CWP without reference to the influence of cigarette smoking. Cigarette smoke is known to inhibit particle clearance [27] and predispose to infection,[95] and there is also a strong association between cigarette smoking in nonminers and chronic bronchitis and emphysema. It is therefore not surprising that the smoking miner is at greater risk for chronic bronchitis and abnormalities of pulmonary function than is the nonsmoking miner.[8, 96] However, smoking does not appear to be a factor that influences the prevalence of CWP determined radiologically. A study of 2,723 British coal miners showed that the incidence of simple CWP was not appreciably altered by smoking.[97] The effect of smoking on PMF was not stated. Very few pathologic studies have taken smoking into account. Naeye et al.[98] studied the effect of cigarette smoking on lung structure in 144 Appalachian bituminous and anthracite coal miners. He found that smoking had no influence on the primary coal dust macule or its direct complications, but bituminous coal miners who smoked had a greater degree of cor pulmonale, more emphysema, and more bronchiolar goblet cells than did the nonsmoking bituminous coal miners. These changes were not seen in the anthracite coal miners. These studies suggest that although cigarette smoking is not directly involved in the pathogenesis of CWP, it does contribute to the overall morbidity from respiratory disease.

PROGRESSIVE MASSIVE FIBROSIS

The term PMF was originally coined by radiologists to describe large opacities in the lungs of coal workers that appeared rapidly and tended to increase in size.[99] The incidence of PMF varies greatly according to local factors, but overall for underground U.S. coal workers it was approximately 0.4 percent in 1975.[8] The condition is associated with an increased mortality from cardiopulmonary disease and for this reason is compensable.

The development of a pathologic definition of PMF has proved difficult for three reasons. First, PMF usually occurs against a background of nodular lesions of varying size with no clear demarcation between the two types of lesion. Second, the nodular lesions of coal workers cannot be distinguished on histologic grounds from PMF. Third, it is not possible to determine at autopsy whether a lesion is progressive or not. Therefore the pathologic definition is arbitrarily based on size. The legal definition as contained in the regulations for the National Coal Workers Autopsy Study [100] defines PMF as a fibrotic lesion greater than 1 cm in diameter. This was chosen to be in accord with the radiologic definition. Recently, however, the Pneumoconiosis Committee of the College of American Pathologists recommended a 2-cm standard as more appropriate for morphologic studies.[43]

Macroscopic Appearance

PMF may be found in all areas of the lungs but occurs most commonly in the upper and posterior portions. It is usually bilateral. The lesions may be round, oval, or irregular in outline and have well-defined borders that clearly separate them from the adjacent lung. Characteristically, they transgress the anatomical boundaries of the lung (Fig. 15). Peripherally situated lesions may be firmly tethered to the parietal pleura. Areas of massive fibrosis that originate in the more central portions of the lung and peripheral lesions that are not attached to the chest wall gradually retract towards the hilum of the lung (Fig. 16). In so doing they may considerably distort the normal lung markings on the chest x-ray (Fig. 16). Solitary PMF lesions are easy to confuse clinically and roentgenographically with neoplasms. In these cases, biopsy or resection may be necessary to confirm the diagnosis.

On cut section, the typical lesion is rubbery to firm in consistency, uniformly black in color, and may show extensive areas of cavitation containing fluid resembling India ink. The liquified contents of these lesions may rupture into an airway during life and give rise to alarming symptoms. PMF is invariably seen against a background of macular or nodular CWP, usually of severe degree. Coalescent nodules of varying size are frequently seen adjacent to areas of PMF (Fig. 15), and these correspond to the ax category of pneumoconiosis on the roentgenogram.[101] Emphysema of focal, scar, bullous, centriacinar, or panacinar types may accompany PMF and varies greatly in amount (Figs. 16, 17). There is no evidence that the extent of emphysema is increased in PMF.[102]

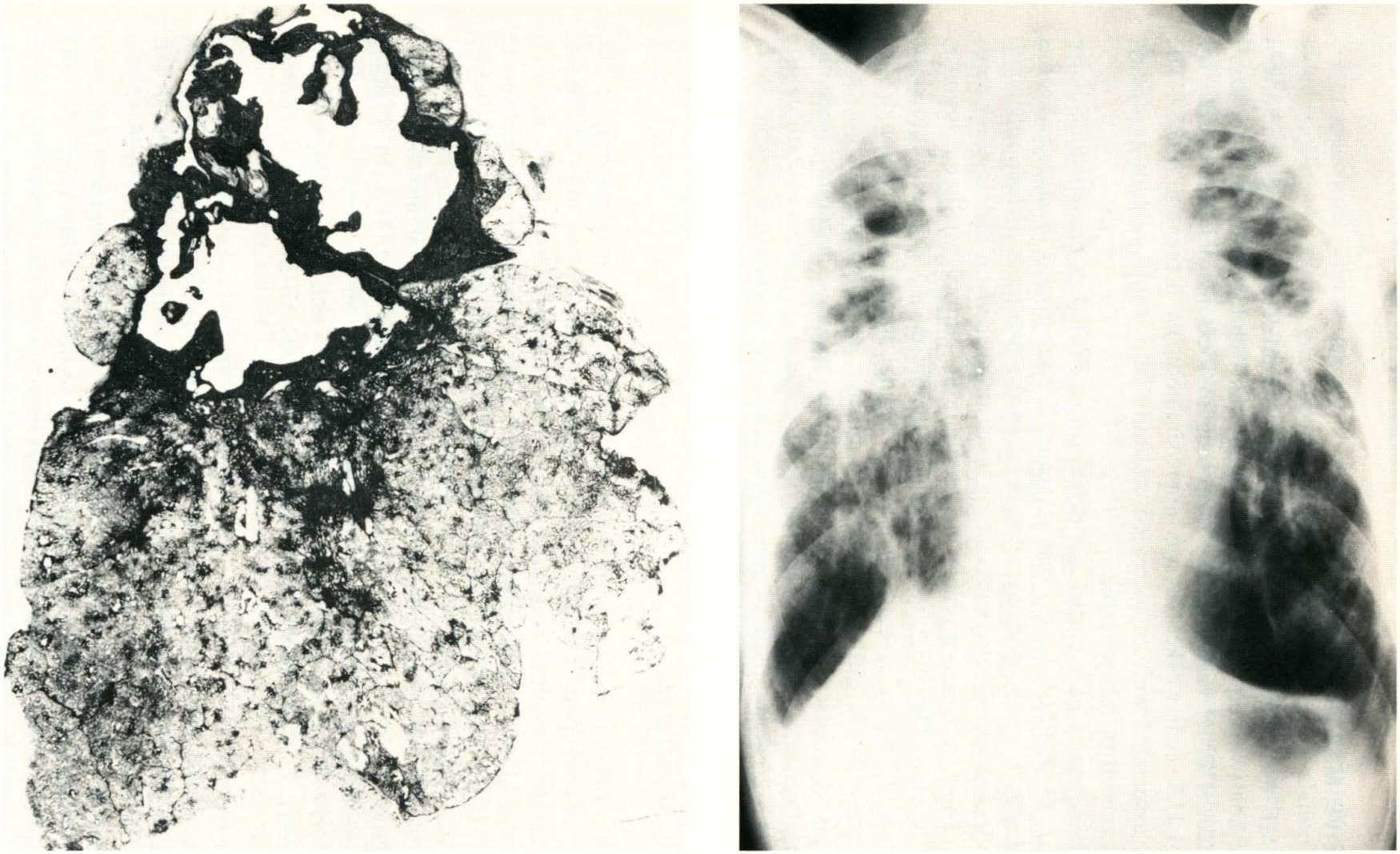


FIG. 15. A 62-year-old Caucasian miner, worked 10 years underground as a loader and 24 years above ground as a checkweighman. **Left.** Whole lung section shows cavitating progressive massive fibrosis. The lesion trangresses the lobar fissure. Micronodules, macronodules, and macules are also present. **Right.** Chest roentgenogram shows bilateral ill-defined opacities consistent with complicated coal worker's pneumoconiosis category B on a background of category 2r round and 2u irregular small opacities. There is marked distortion of the pulmonary vessel markings.

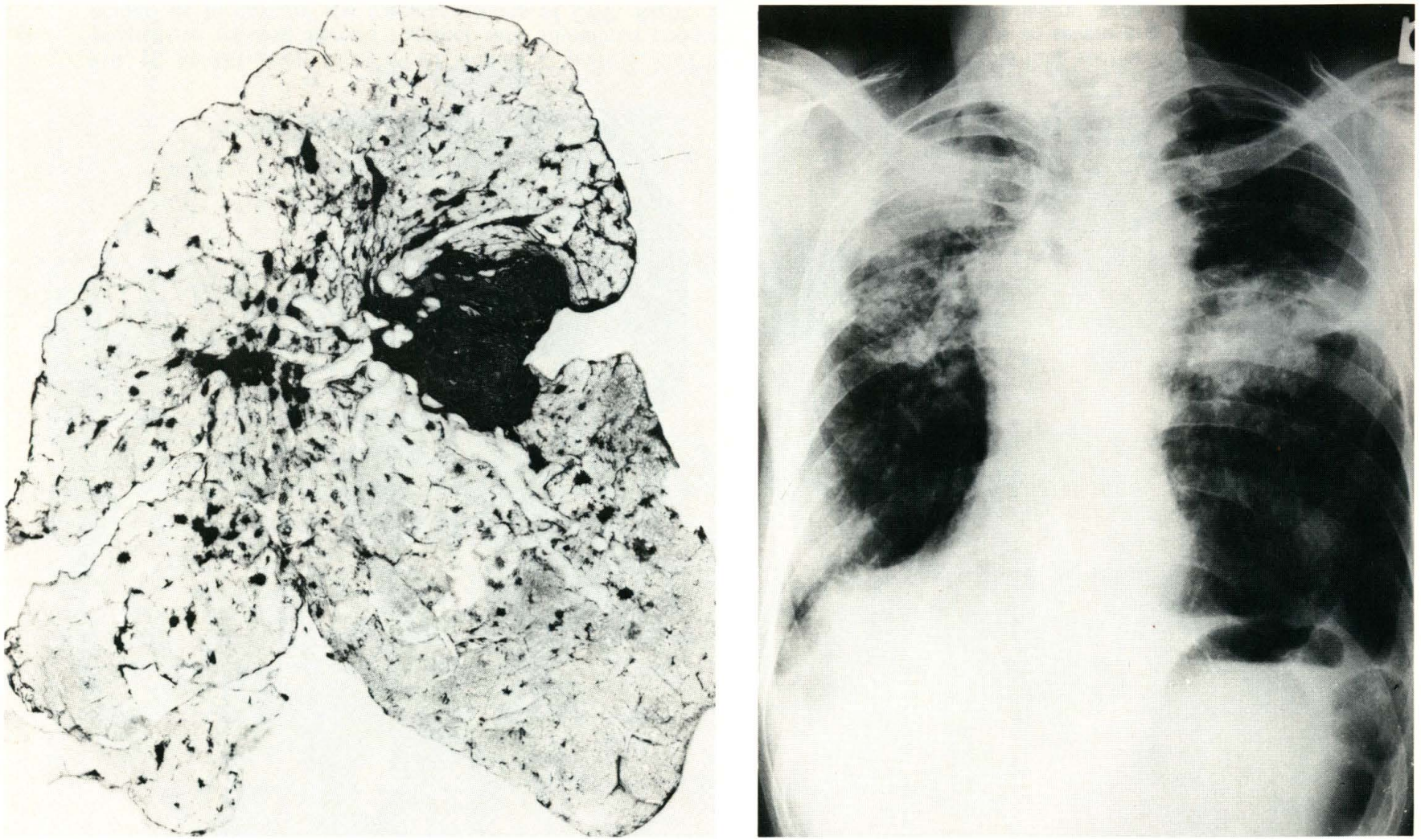


FIG. 16. Coal miner, worked 35 years underground, nonsmoker. **Left.** Whole lung section shows progressive massive fibrosis (PMF) on a background of nodular and macular disease. The PMF lesion has retracted toward the hilum. **Right.** Chest roentgenogram shows bilateral upper zone large opacities consistent with complicated pneumoconiosis B on a background of category 2r small opacities.

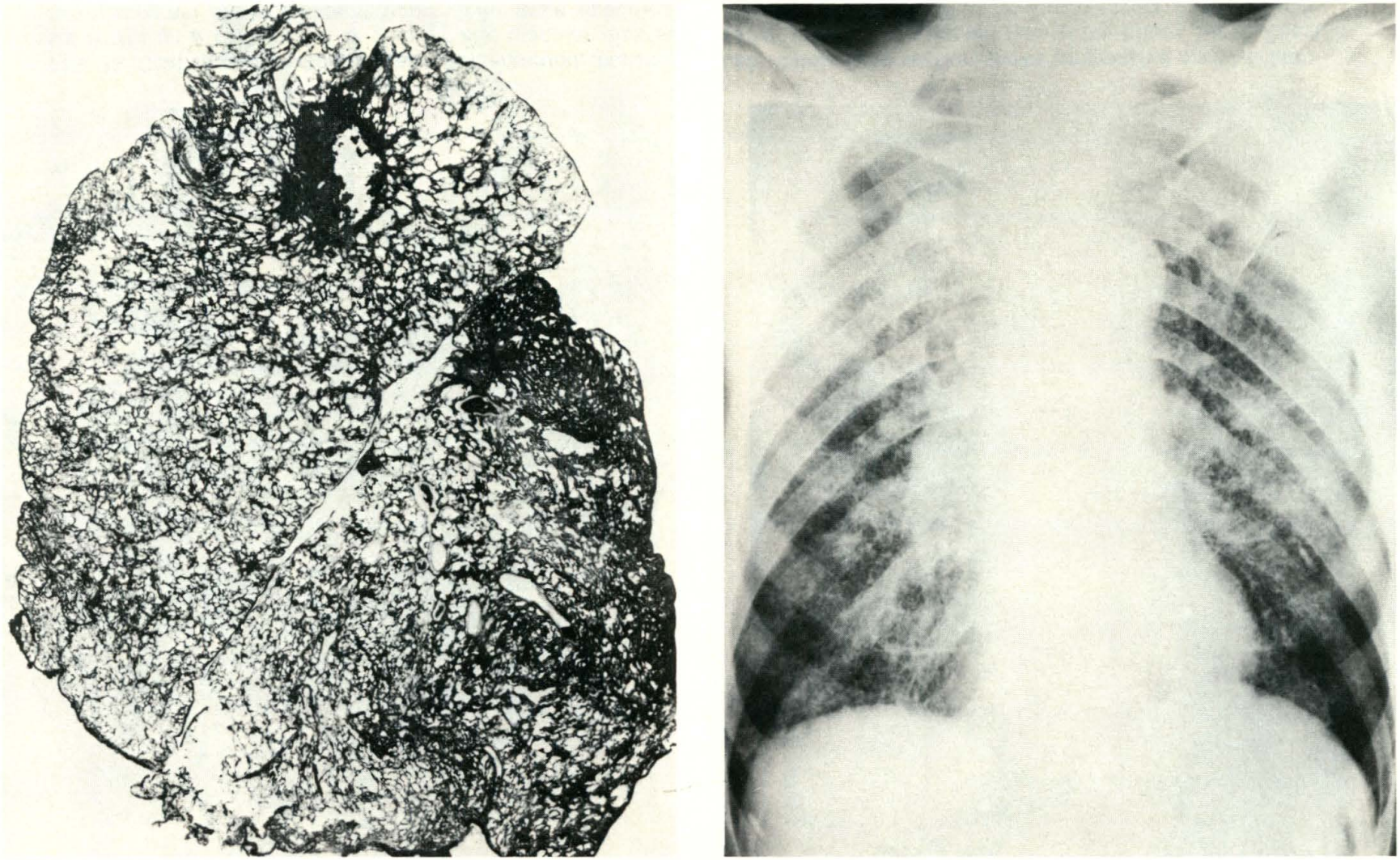


FIG. 17. An 83-year-old black miner, worked 47 years as coal loader, nonsmoker. **Left.** Whole lung section shows cavitating progressive massive fibrosis together with ill-defined nodular lesions. The emphysema is so severe and extensive (panacinar) as to obscure the macular lesions of CWP. **Right.** Chest roentgenogram shows bilateral large opacities consistent with category B complicated pneumoconiosis on a background of category 3q small opacities. Comment: there is no evidence that the emphysema has interfered with the radiologic recognition of pneumoconiosis.

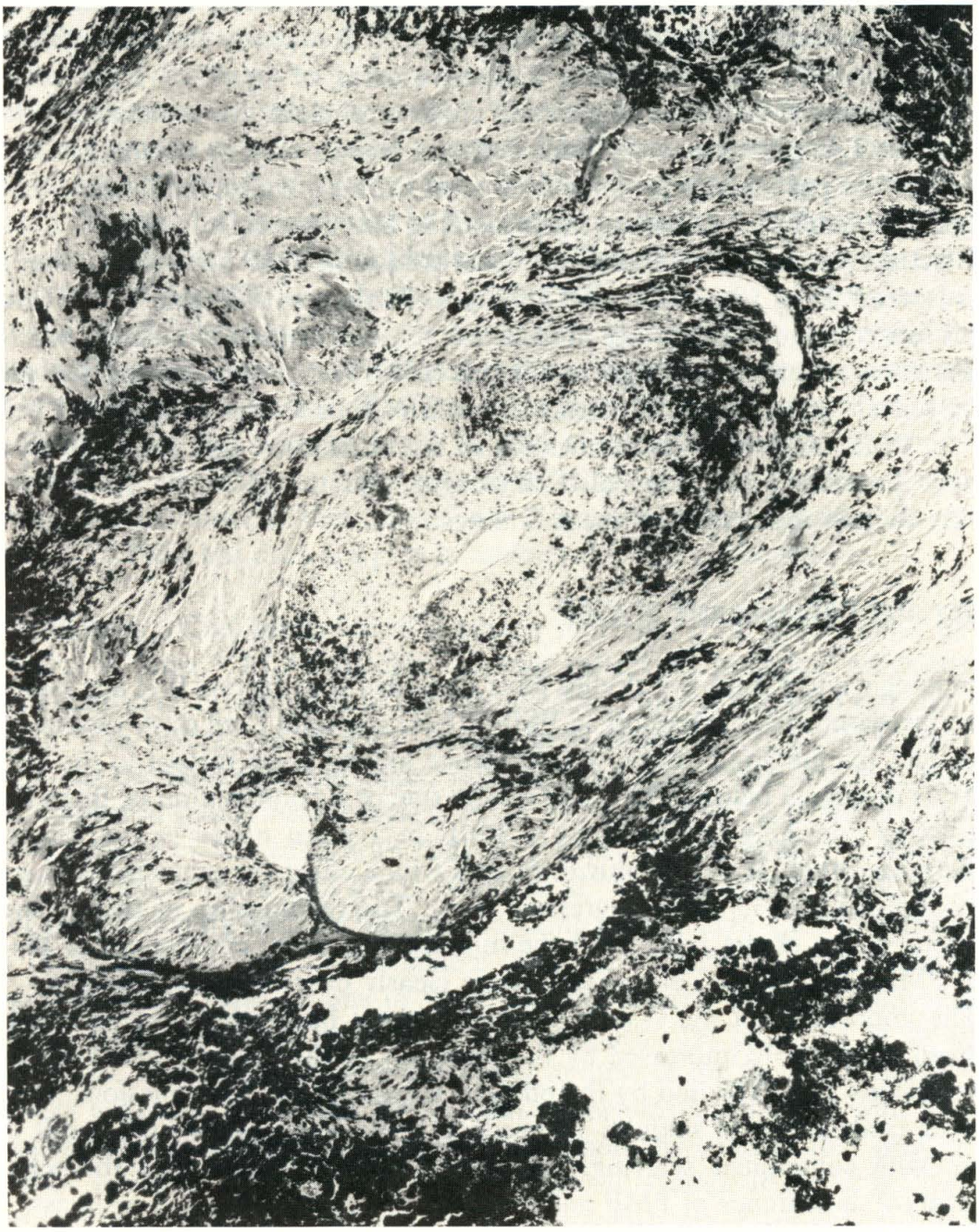


FIG. 18. Progressive massive fibrosis, showing coal-dust-containing macrophages lying between bundles of hyalinized, haphazardly arranged collagen. A large vessel, at center, has been almost entirely replaced by fibrous tissue and pigmented macrophages. Note the cavity containing free dust at lower field. H&E. ×180.

Microscopic Appearance

The lesions are composed of bundles of haphazardly arranged hyalinized collagen and reticulin fibers in which masses of coal dust are embedded (Fig. 18). The dust particles near the periphery of the lesion are mainly within macrophages, whereas in the center the dust tends to lie free in clefts and cavities between the connective tissue fibers. Hyalinized nodules showing features of silicosis are seen in some cases.

Special stains reveal the remains of obliterated arteries, veins, and bronchi in the center of the lesions. Blood vessels at the periphery frequently show an obliterative vasculitis (Fig. 18) and thrombosis. Extensive areas of liquefactive necrosis containing fragments of necrotic collagen and cholesterol clefts are associated with vascular lesions. Lymphocytes and plasma cells are seen in varying numbers in massive fibrosis and are particularly prominent in cases showing widespread vasculitis. Special stains are helpful in excluding mycobacterial and mycotic infection.

Electron microscopical and biochemical studies in PMF have shown that these lesions contain 20 to 50 percent coal and up to 30 percent collagen.[57, 103] The latter figure is low compared with other fibrotic lesions such as pleural plaques, where the collagen content may be as high as 90 percent.[57] The proportions of the glycosaminoglycans, hyaluronic acid, dermatan sulfate, chondroitin sulfate, and heparin sulfate in PMF, however, were indicative of active fibrosis. Qualitative analysis of the other proteins present revealed fibrinogen and the globulins IgA and IgG. Electron microscopy supported these findings.

Etiology and Pathogenesis of PMF

Epidemiologic and pathologic studies have identified four factors that are associated with an increased risk of developing PMF. These are total lung dust, quartz, tuberculosis, and immunologic status. The evidence linking these factors to the etiology of PMF is discussed below. The value of any one or a combination of these factors in predicting the likely development of PMF in a given miner is low, suggesting that there are other, as yet unknown, factors which effect the conversion of simple pneumoconiosis into its more aggressive form. The relationship of factors such as the genetic status of the miner and the mineral and metal component of the coal dust to PMF are discussed elsewhere. These clearly deserve more attention.

The importance of the vascular lesions has not been adequately stressed. We have been particularly impressed by the similarity of the vascular abnormalities in nodular lesions and PMF and by the physical proximity of the two lesions. Increase in size or coalescence of nodules to produce PMF could occur as a result of infarction with subsequent scarring. This mechanism would explain the relatively rapid clinical appearance of PMF and the tendency of the lesions to progress.

TOTAL LUNG DUST. The early observation by James [104] that PMF was not related to duration of exposure and hence to lung dust content has not been borne out by subsequent studies. It is now generally agreed that PMF occurs against a background of higher radiologic categories of simple pneumoconiosis.[105-109] The frequency of progression to PMF (attack rate) was determined on 105,000 working British coal miners by McLintock et al.[108] They found that the attack rate increased with advancing simple pneumoconiosis on the earlier film, with rate of progression of simple pneumoconiosis, and with total dust exposure. Silica exposure was not found to be a significant factor. Autopsy studies in the United Kingdom [68, 70, 110] and the United States [69] have shown a direct correlation between dust content of the lung and the severity of pneumoconiosis.

QUARTZ. PMF is a frequent complication of classical silicosis and occurs more commonly in silicosis than in CWP.[110] Miners in the anthracite coal fields of Pennsylvania [104] and South Wales [111] have a high incidence of PMF, which is thought to be related to increased silica exposure.[6,.110] Autopsy studies have shown a greater total quartz content of the lungs in cases with PMF than in those with the lower categories of simple CWP.[69, 70, 112, 113] There is also evidence that the concentration of quartz in the total dust is increased in PMF and that quartz is preferentially retained in lungs that show the more severe lesions.[69, 70] There are several reasons for doubting the theory that silica is the cause of PMF. First, the association between silica and PMF noted previously also applies to nonquartz minerals. Second, post-mortem studies have shown that there is a very wide range in the amount of silica in the lungs of cases with PMF, suggesting factors other than silica are operative. Third, PMF has been reported in coal trimmers,[58] carbon electrode,[54] and carbon black workers,[53] where exposure to silica is negligible. Our conclusion from reviewing the literature is that quartz is a factor which sets the stage for the development of PMF but does not play a unique role in its pathogenesis.

TUBERCULOSIS. Coal miners have a greater mortality from tuberculosis than the population at large.[62] In Appalachia this may reflect the historical prevalence and delayed control of tuberculosis in the region rather than an elevated risk due to occupation. The percentage of PMF lesions from which tubercle bacilli have been isolated has declined over the years, reflecting the general decline in tuberculosis due to improved public health measures. In 1954, James [104] isolated mycobacteria from 40 percent of 454 cases with PMF at autopsy. Rivers et al.[114] cultured bacilli from 35 percent of cases with PMF. Naeye et al.[6] found acid fast bacilli in 17 percent of the pulmonary nodular lesions measuring greater than 1 cm in diameter in a series of Pennsylvania anthracite miners. Laqueur [115] cultured mycobacteria from 7.5 percent of the PMF lesions in West Virginia miners who died between 1956 and 1962. In 41 percent of these cases, the organism was classified as an atypical mycobacteria. This observation is interesting in view of the fact that Marks [116] had previously suggested PMF may result from opportunistic infection with mycobacteria of low virulence. Experimental studies support the concept that coal dust enhances the virulence of *Mycobacterium tuberculosis*. Gernez-Rieux et al.[117] exposed guinea pigs to combinations of coal dust and mycobacteria. They demonstrated that the severity of the lesions was dependent on both the amount of coal dust and the concentration of quartz. Other studies have confirmed the synergistic effects of coal dust [118] and silica [119-121] on experimental tuberculosis. These effects may be related to the toxic effects of silica on the macrophage.[122] The evidence presented above suggests that a proportion of PMF cases are associated with mycobacterial infection and that this is enhanced by concomitant silica exposure. The evidence linking tuberculosis and PMF has weakened over the years. No difference in tuberculin sensitivity could be detected between miners with PMF and miners with either simple pneumoconiosis or no pneumoconiosis.[123, 124] Moreover, controlled trials of antituberculous chemotherapy in the early stages of complicated CWP have failed to prevent progression of the disease.[125, 126]

IMMUNOLOGIC FACTORS. The observation by Caplan [127] that a distinct form of complicated pneumoconiosis may occur in coal workers with rheumatoid arthritis has stimulated research into the role of immunologic mechanisms in the pathogenesis of PMF. A study in England showed an increased frequency of RF in the serum of miners with PMF as compared with miners with simple CWP,[91] though a similar study of Appalachian miners failed to confirm the association.[92] Wagner and McCormick [128] investigated the distribution of RF in the lesions of PMF by immunofluorescence. They found the majority of lesions showing an active vasculitis with plasma cell cuffing also contained RF. Rheumatoid factor was found only in 20 percent of PMF lesions without vasculitis and in the same percentage of the lesions of simple CWP. They suggested there may be two distinct types of PMF, one of which would represent an atypical form of rheumatoid pneumoconiosis. Immunoglobulins have been demonstrated in the lesions of PMF, but their significance is not known.[57, 103] Cell-mediated immunity has not to our knowledge been investigated in this condition.

RHEUMATOID PNEUMOCONIOSIS (CAPLAN'S SYNDROME)

Background

In 1953 Caplan [127] reported an increase in severe pneumoconiosis in Welsh coal miners with rheumatoid arthritis (RA). His findings, based on the examination of approximately 14,000 chest roentgenograms, showed PMF in 90 percent of 51 miners with RA compared with an incidence of 30 percent in miners without RA. The roentgenograms of the arthritics showed large, evenly distributed, and well-defined nodular opacities that were not typical of either simple CWP or silicosis. The unique morphologic characteristics of these lesions were later described by Gough et al.[129]

The prevalence of Caplan's syndrome for all working miners in Europe is approximately 1 percent. However, for miners who have clinical RA, the prevalence is approximately 30 percent.[130] Caplan's findings have been well confirmed in Great Britain [51] and in the Ruhr bituminous region of Germany.[131] The situation in the United States appears to be different. The syndrome undoubtedly occurs but appears to be uncommon. Benedek et al.[132] studied 100 active and retired Pennsylvania bituminous miners with RA who had an average duration of 31 years in underground mining. Only three cases showed radiographic evidence of Caplan's syndrome; moreover, no evidence was found that RA exerted a deleterious effect on either the frequency or severity of pneumoconiosis in comparison to published prevalence data on U.S. miners.

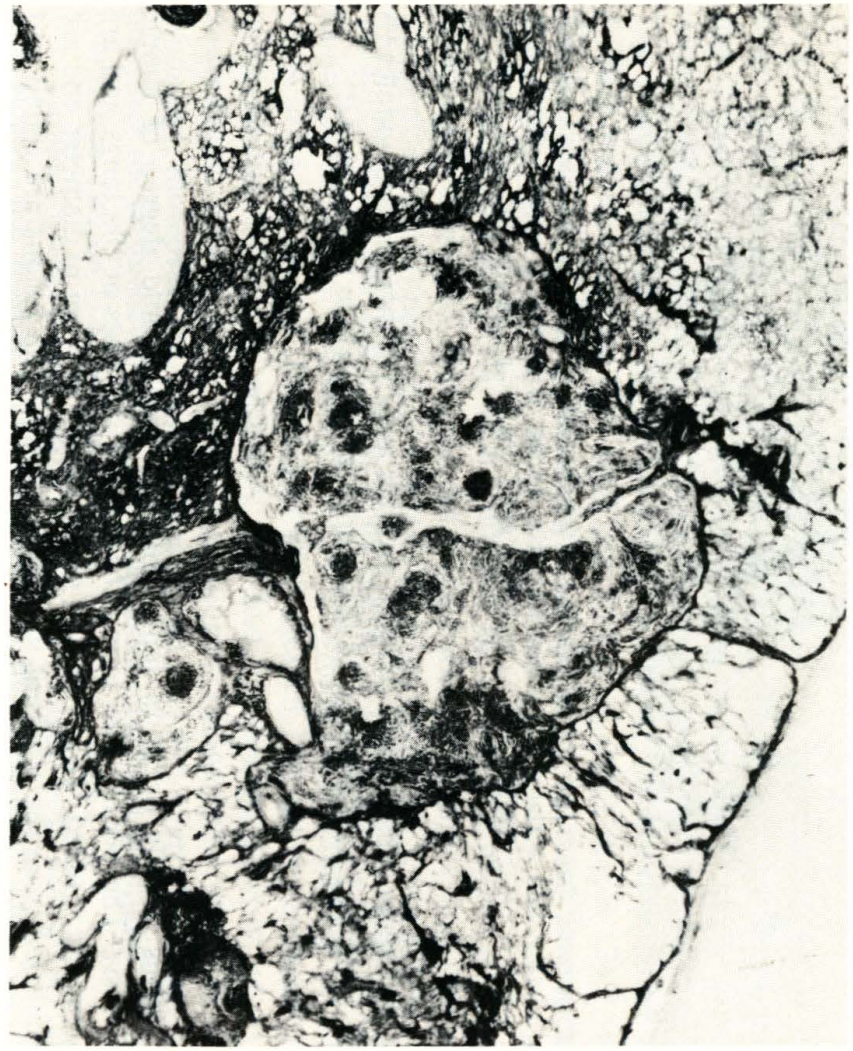
Caplan's syndrome occurs in miners of all ages, both active and retired. Radiologically, the lesions progress more rapidly than PMF and may show ring shadows, cavitation, and areas of calcification. Rapidly fatal fulminating forms of the disease have been recorded.[51] The typical radiographic features of Caplan's syndrome may be seen in miners without clinical evidence of rheumatoid arthritis.[133] In these cases a circulating rheumatoid factor is invariably present, and follow-up

FIG. 19. A 63-year-old Caucasian miner, worked 24 years underground as machine operator, no smoking history, had active rheumatoid arthritis. **Above.** Whole lung section shows several large, well-circumscribed, Caplan nodules. Mild macular disease is also present. (Continued)

has shown that many subsequently develop arthritis and/or subcutaneous nodules.[132] Caplan has expanded his definition of the syndrome to include these cases.[134]

Pathology

Caplan's lesions usually occur in lungs showing only a mild degree of simple pneumoconiosis. The nodules are found throughout all lobes of the lungs and are often peripherally situated. They range in size from 0.5 to 5 cm in diameter and are clearly delineated from the adjacent lung parenchyma. The lesions are round and discrete but may form larger confluent masses (Fig. 19). On sectioning, the smaller nodules show concentric laminations of alternating pale yellow and dark areas. Liquefaction and cavitation of the lesions' centers are common, and calcification is seen in longstanding cases. Areas of interstitial fibrosis and honeycombing may be present.



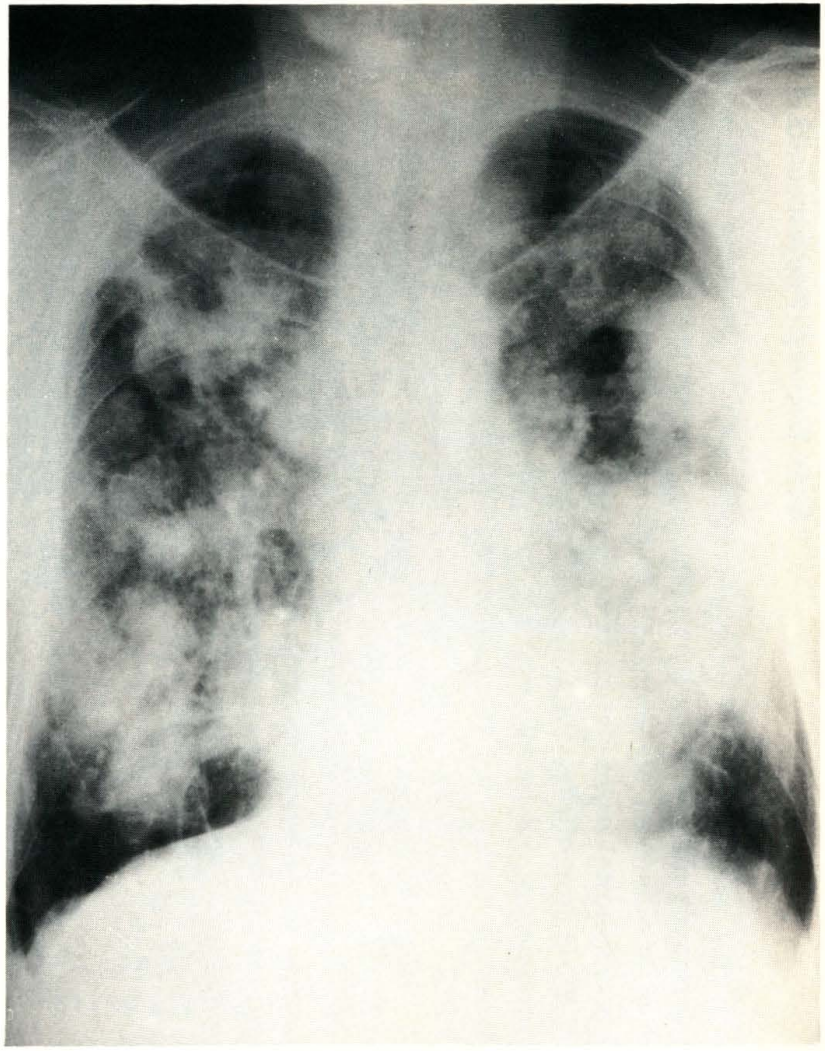


FIG. 19 (cont.) Left. Close-up of Caplan's lesions showing pale (necrotic) areas with islands and rings of dust. The lesion is encapsulated. **Right.** Chest roentgenogram, shows numerous large round opacities typical of Caplan's lesions (complicated pneumoconiosis category C) against a background of category 1q small opacities.

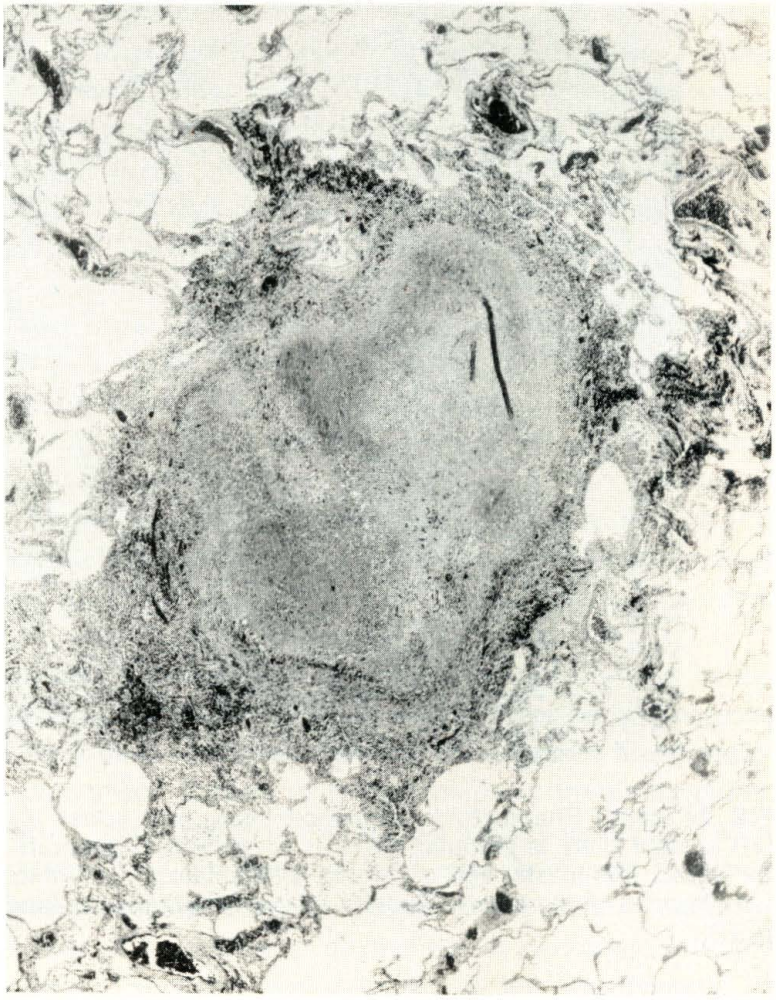


FIG. 20. Rheumatoid pneumoconiosis (Caplan's lesion), low-power view. The nodule is composed of an area of central necrosis surrounded by a ring of dust and chronic inflammatory cells. The scanty pigmentation is typical. H&E. ×15. (Continued)

Microscopically, the active lesions have some features in common with rheumatoid nodules encountered in the subcutaneous tissues and in the lungs of non-coal-miners with RA.[135] The center of the typical Caplan's lesion is composed of eosinophilic necrotic material containing nuclear debris, polymorphs, and fragments of reticulin and elastic fibers. Stains for "fibrinoid" are usually negative.[129] Cholesterol clefts are common in the older lesions. The necrotic center is surrounded by a cellular layer composed of macrophages and fibroblasts. These may be arranged in palisade formation (Fig. 20). Giant cells are infrequnt. Occasional nodules are encountered containing considerable numbers of polymorphonuclear cells. These may indicate a more active phase of the lesion. The periphery of the nodule is composed of concentrically arranged collagen fibers and fibroblasts in which numerous plasma cells and lymphocytes are enmeshed. Blood vessels within the lesion and adjacent to it frequently show endarteritis obliterans with lymphocytic and plasma cell infiltration of their walls. The laminations noted macroscopically are composed of bands of coal dust pigment, most of which is extracellularly located. It has been suggesed that these dust rings result from the migration of successive waves of coal-dust-laden macrophages during periods of activity, with subsequent release of the pigment following macrophage death.[51] Older inactive lesions show central calcification with more closely spaced rings of dust in a dense collagenous stroma.

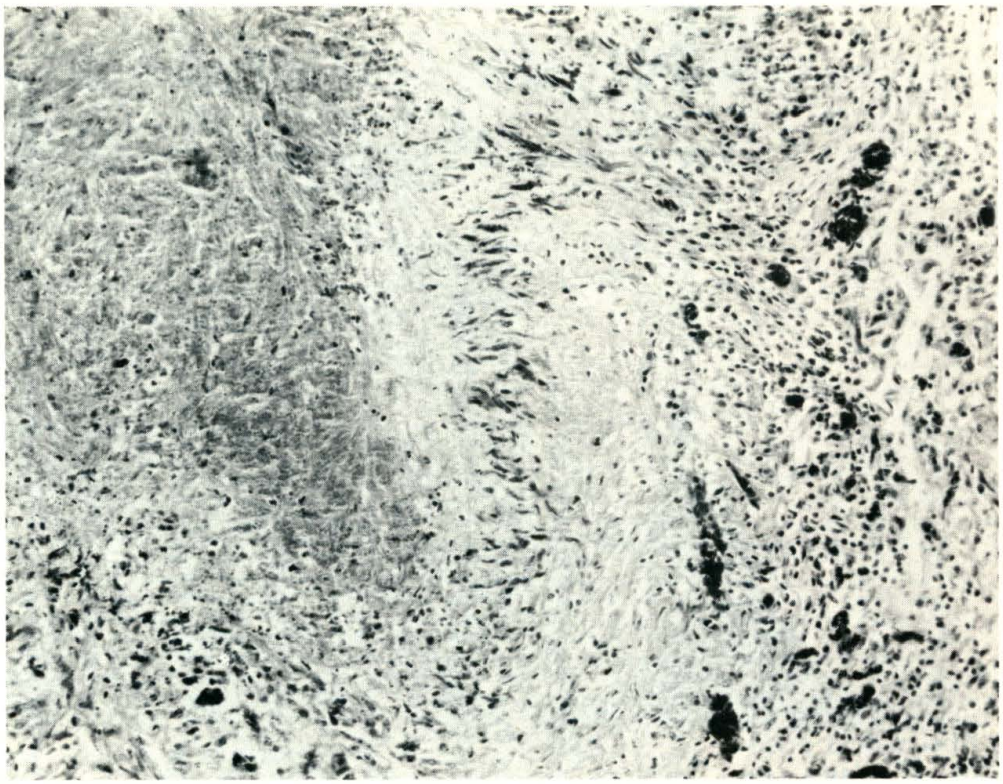


FIG. 20 (cont.) Rheumatoid pneumoconiosis, high-power view from edge of lesion. From left to right there is granular necrosis containing degenerate polymorphonuclear leukocytes, palisaded fibroblasts, and a chronic inflammatory cell infiltrate in which plasma cells and lymphocytes predominate. Special stains for organisms (and cultures) were negative. H&E. ×300.

Caplan's lesions need to be distinguished from those of tuberculosis and silicosis. The older Caplan's lesion may be impossible to distinguish histologically from silicotic nodules. In these cases, chemical or microanalytical procedures for silica may be helpful. Silicotic lesions are usually smaller than Caplan's lesions, and central necrosis is less common. Palisading of fibroblasts, plasma cell infiltration, and cholesterol clefts are not usual features of silicosis. Tuberculous lesions are usually found in the upper lobes and are rarely as well circumscribed as Caplan's lesions. Histologically, Caplan's lesions and tuberculous lesions have many features in common, but dust rings are less common in tuberculosis, and plasma cells, which are abundant in Caplan's lesions, are exceedingly rare in tuberculosis. Special stains for fungi and mycobacteria may be of value in differentiation, as may culture of the fresh lesion.

Pathogenesis

The observation that Caplan's lesions may precede the onset of arthritis by several years [133] raises the possibility that CWP predisposes to the development of RA. This is unlikely for two reasons. First, RA is no more common in coal workers than in the population at large.[136] Second, Caplan's lesions do not appear to antedate the presence of RF in the serum.[133]

Rheumatoid lesions of the lung are rare in individuals not exposed to dusty environments. The relationship of coal dust to the development of the lesions is not simple. The lesions of Caplan's syndrome, unlike PMF, characteristically occur against a background of little dust and mild simple pneumoconiosis. If the amount of dust is not a significant factor in the genesis of the lesion, then some specific constituent may be. The observation that similar lesions are associated with a variety of mineral pneumoconioses has led to the suggestion that silica may be this factor.[130]

Infectious agents have also been implicated in the pathogenesis of Caplan's lesions. Gough et al.[129] identified tubercle bacilli in the lesions of 3 of the 14 cases they described and suggested the lesions resulted from a modified reaction to tubercle bacilli. The association of Caplan's lesions and tuberculosis has been disputed by Parkes.[51] The observation by DeHoratius [137] that pulmonary lesions induced in rabbits by Freund's adjuvant could be enhanced by subsequent treatment with RF lends some credence to the tubercle theory. On the other hand, the same findings would equally well support the idea that Caplan's lesions result from immunologic mechanisms.

The histologic resemblance of Caplan's lesions to rheumatoid nodules in the subcutaneous tissues points to a common underlying mechanism for both. Necrosis, granulomatous inflammation, and immunocompetent cells all suggest a hypersensitivity reaction. Necrosis is a recognized feature of hypersensitivity involving either cellular or humoral mechanisms. Granulomatous lesions are usually associated with delayed hypersensitivity; however, they can be produced experimentally in rabbit skin by the injection of preformed immune complex formed at the zone of antigen/antibody equivalence.[138] It is thus not possible to determine on histologic grounds alone whether cellular or humoral reactions are involved in the pathogenesis of Caplan's lesions. Immunoglobulins, including RF, have been demonstrated immunohistochemically in the plasma cells of the pulmonary rheumatoid lesions of coal workers [128] and non-coal-workers,[139] and IgM has been observed in the walls of arteries adjacent to Caplan's lesions.[128] It has been suggested that coal dust may provide a local stimulus for the production of immunoglobulins. This is based on the observation that following the injection of coal dust into the foot pads of rabbits, macroglobulin-containing cells appeared in the inguinal lymph nodes. Some of the globulins had RF-like specificity.[99] Local synthesis of immunoglobulins with deposition around dust foci, possibly as immune complex, could be the starting point for subsequent cellular events. The vasculitis and polymorphonuclear cell infiltrate would further suggest that complement has been activated, though this was not observed in the nodular rheumatoid lesions of non-coal-miners.[139] Electron microscopic studies would appear to be a logical next step in the study of these lesions. These could throw light on the relative importance of dust, infection, and immune mechanisms in the pathogenesis of this disease.

INTERSTITIAL FIBROSIS

Areas of diffuse, pigmented interstitial fibrosis with honeycombing may be seen in the lungs of coal workers (Figs. 21, 22). In our experience the entity is rare. It

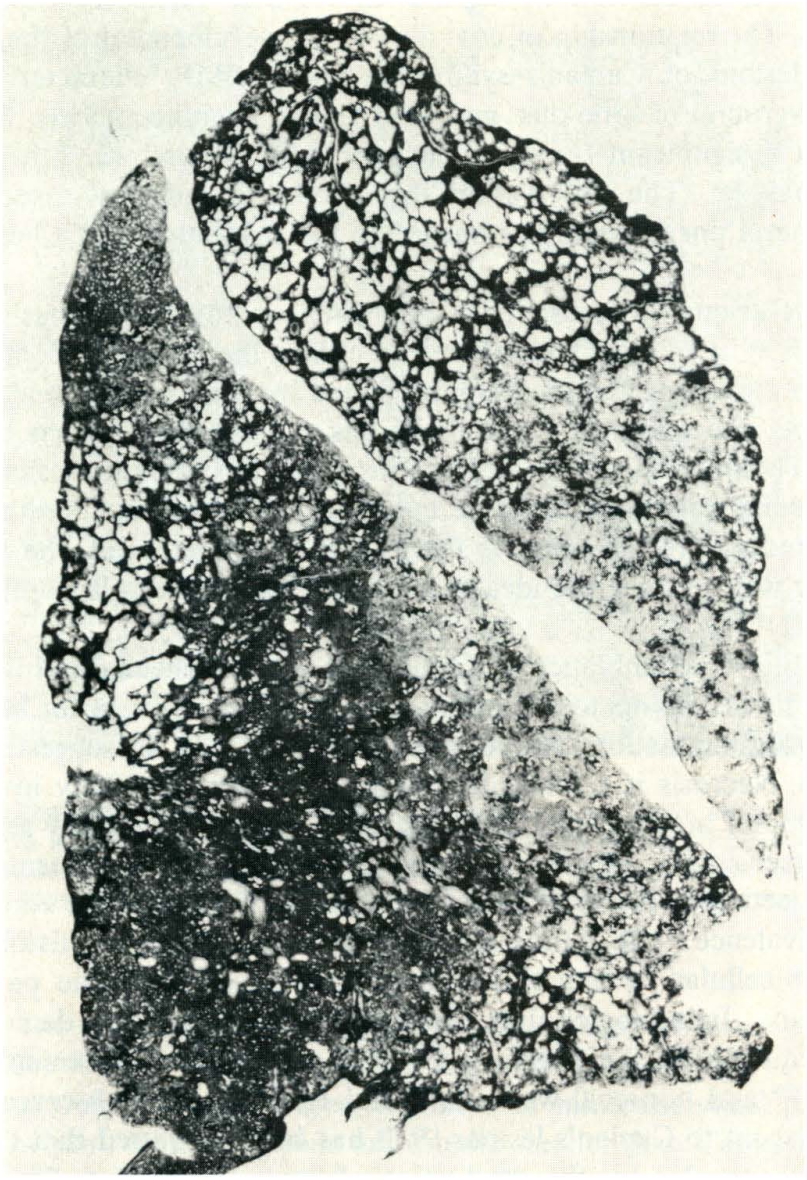


FIG. 21. A 72-year-old black miner, worked 50 years in mines at a variety of jobs, including trapper, motorman, checkweighman, and coal loader. Nonsmoker. Whole lung section shows marked interstitial fibrosis with cyst formation (honeycombing). The areas of interstitial fibrosis are deeply pigmented. Elsewhere the lung shows mild macular disease.

should not be confused with diffuse dust deposition in emphysematous lungs or with certain cases of nodular disease with extensive scar emphysema. It is reported that interstitial fibrosis occurs more frequently in association with Caplan's syndrome.[51]

SILICOSIS IN COAL WORKERS

The incidence of silicosis among coal workers has not been well documented. In a series of autopsied coal workers from southern West Virginia, 13 percent showed histologic evidence of silicosis.[115] In the majority of cases, silicotic nodules are an

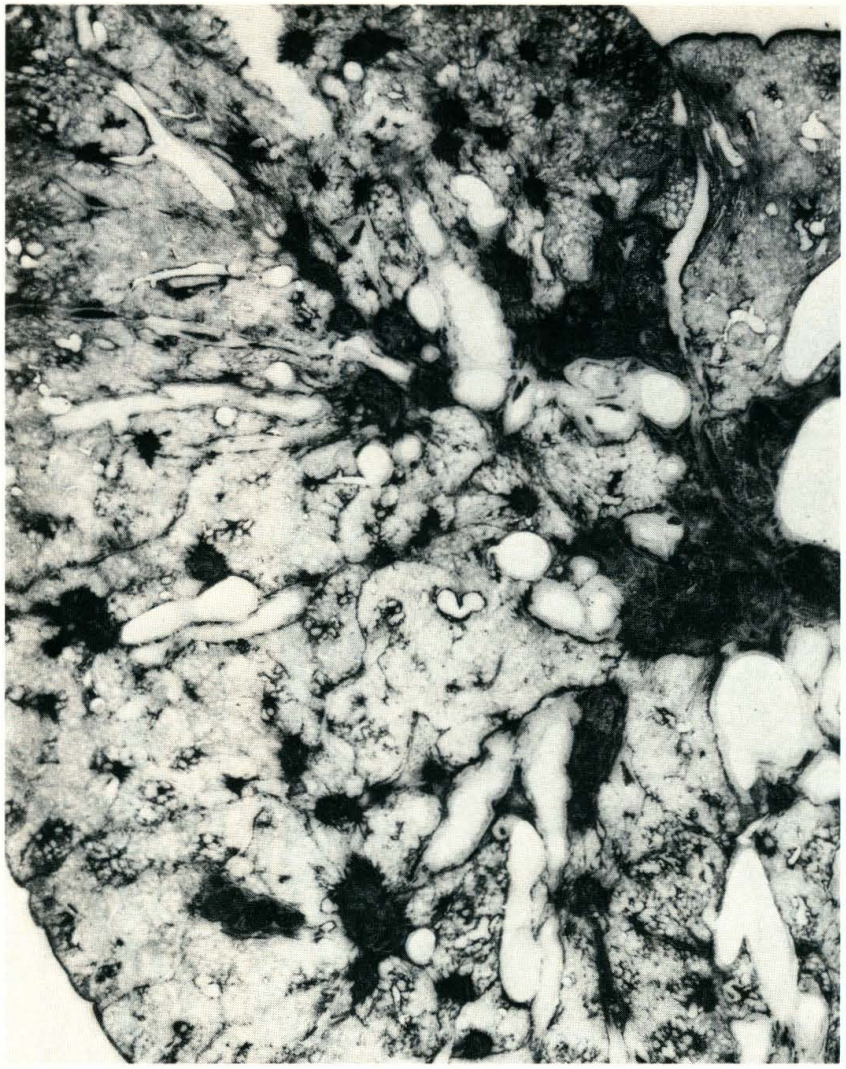
FIG. 22. Interstitial fibrosis. The dust is distributed around small vessels and within the alveolar walls. Typical macular and nodular lesions were not seen. H&E. ×98.

incidental finding at autopsy and occur in conjunction with the macular and nodular lesions of CWP. They occur more frequently in the hilar lymph nodes than in the lung parenchyma. The nodules are usually of uniform size, are more firm, and have smoother borders and paler centers than the typical nodules of CWP (Fig. 23). Calcification is common, particularly in the hilar lymph nodes, which gives the characteristic "eggshell" appearance to the chest x-ray.[140] Silicotic nodules tend to

FIG. 23. A 60-year-old Caucasian miner, worked 30 years underground as brakeman and motorman; cigarette smoker. **Above.** Whole lung section shows numerous round nodular silicotic lesions which are more numerous in the upper zone. Coalescence of nodules has resulted in early progressive massive fibrosis. There are also macular lesions with focal emphysema. (Continued)

coalesce to produce PMF. The silicotic PMF lesion is firm to hard in consistency and contains numerous small pale nodules (Fig. 24).

Histologically, the mature nodule is composed of concentrically arranged laminations of collagen fibers surrounding a hyalinized center (Fig. 25). The silica and coal dust particles tend to be concentrated at the periphery of the lesion. Crystalline silica or quartz is only weakly birefringent and requires a properly equipped polarizing microscope for identification. The more brightly birefringent silicates, which are less fibrogenic than quartz, are common in the pulmonary lesions of coal workers. It is important, therefore, to differentiate these two types of particles when making a diagnosis of silicosis.



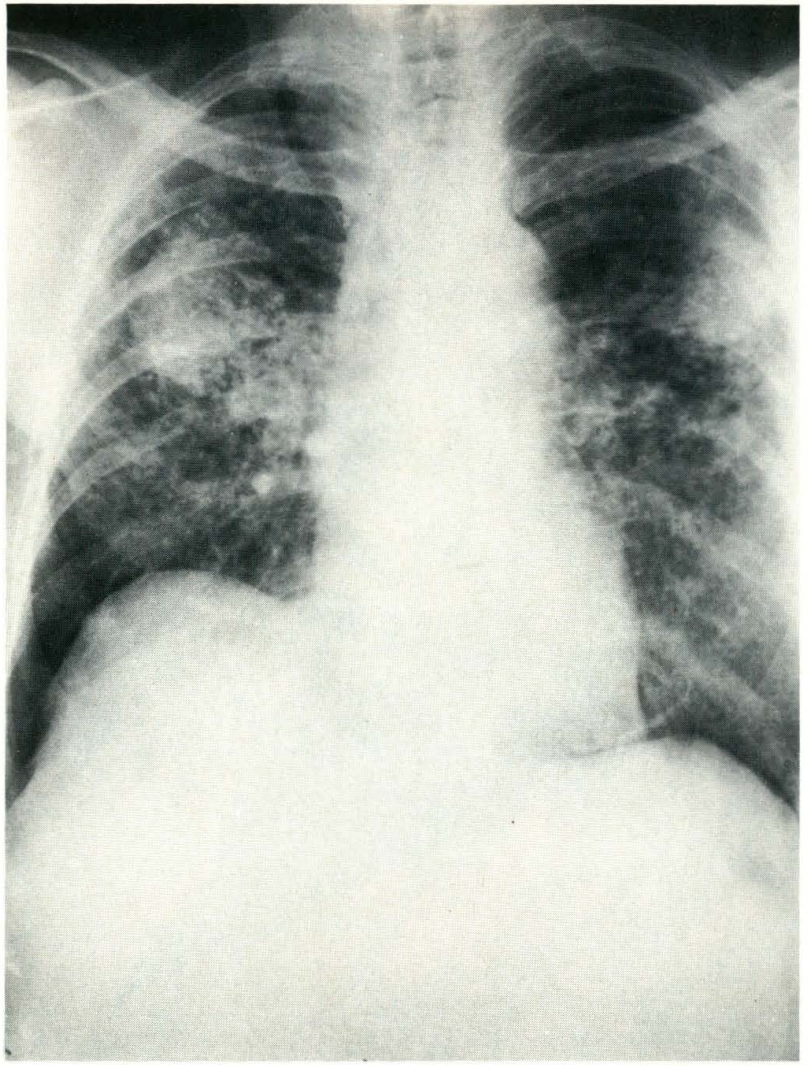


FIG. 23 (cont.) Left. Close-up, the nodules are of uniform size, have pale centers, and show little scar emphysema. The outline of the nodule is preserved in areas showing coalescence. **Right.** Chest roentgenogram shows bilateral category B complicated pneumoconiosis against a background of category 3r small opacities. There is calcification of hilar lymph nodes. Comment: Locomotive operators have a high incidence of silicosis.

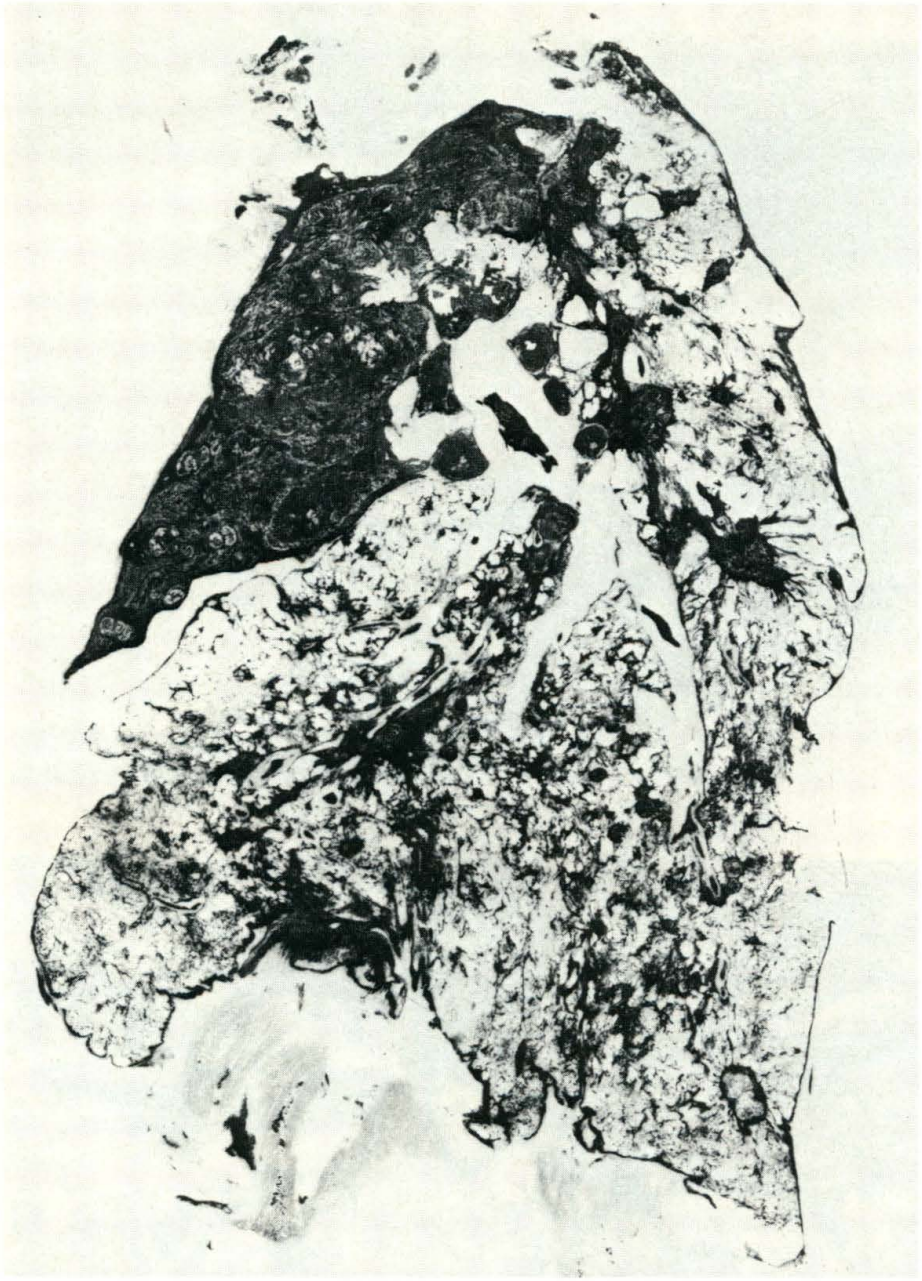


FIG. 24. Coal worker, no case details. Whole lung section shows progressive massive fibrosis set against a background of nodular and macular disease. The pallor of the nodules, and their preservation in the area of massive fibrosis are indicative of silicosis. This was confirmed by histologic examination.

EMPHYSEMA IN COAL WORKERS

Emphysema is an anatomic condition which can be classified into panacinar (panlobular), centriacinar (centrilobular), focal, alveolar duct, paraseptal, and irregular (including scar) types according to its location. Focal and scar emphysema, previously discussed, are closely related to the respective macular and nodular lesions of CWP. The functional significance of focal emphysema and the extent to which the

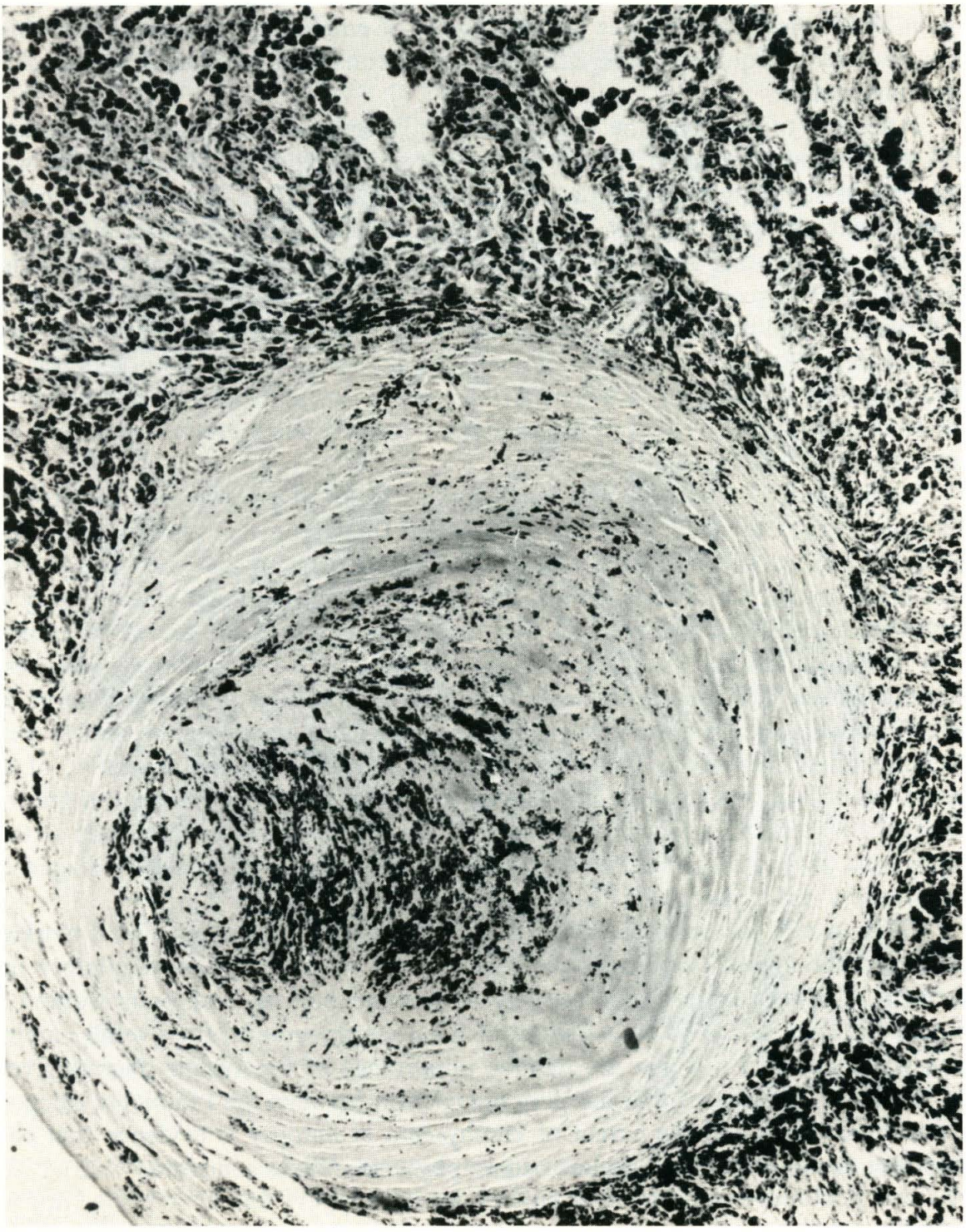


FIG. 25. Silicotic nodule in a coal miner. The concentric arrangement of the collagen fibers is characteristic. Dust is concentrated in the center and periphery of the lesion with a relatively dust-free zone between. Special stains should be used to exclude histoplasma or other infective granulomata. Positive identification of silica in the lesions requires electron microscopy combined with x-ray analysis and selected-area electron-diffraction procedures. H&E. ×195.

mining environment contributes to other forms of emphysema are questions which have not been adequately resolved. They are of considerable clinical and medicolegal importance.

Attempts to compare the amount of emphysema in autopsied coal workers with the general population have been hampered by technical difficulties and with problems in sampling methodology. Naeye et al.[98] found the lung area comprised of abnormal air space was 24.3 percent in nonsmoking Appalachian bituminous coal workers as compared with approximately 30 percent in cigarette smoking miners and 4.8 percent in an age- and sex-matched control population composed of both smokers and nonsmokers. The type of emphysema was not determined. Thus it is not clear whether the increase in emphysema seen in the coal workers was related to the dust lesions or independent of them. Also, the study was retrospective and consequently suffered from the limitation that the emphysema index was determined on uninflated lung.

Ryder et al.[102] studied whole lung sections from 247 Welsh coal miners and 247 age- and sex-matched controls. They found that the extent of the emphysema in the miners correlated closely with ventilatory impairment and with fine punctiform markings on the radiograph but not with increasing radiographic category of pneumoconiosis. They also showed that there was a significant excess of emphysema in the miners for all age groups when compared to the controls. However, their conclusion that the prevalence of emphysema is greater in miners than in the general population was not entirely justified, since the majority of the miners were receiving disability benefits and were therefore probably not representative of all miners. Moreover, the smoking histories of the nonminer controls were not known. Perhaps the most important conclusion that can be drawn from this study is that emphysema plays a major role in the disability associated with clinically diagnosed coal workers' pneumoconiosis.

Glick et al.[47] analyzed the data from a series of 700 Australian coal workers and found the extent of post-mortem emphysema correlated with ventilatory impairment, a history of smoking, severity of pneumoconiosis, and years worked at or near the coal face. The contribution of focal emphysema to the overall emphysema was not stated nor was the relative importance of the various factors given.

Parkes [51] has argued that the poor correlation between the radiologic category of pneumoconiosis and the extent of emphysema at autopsy is evidence that coal mine dust is not etiologically related to emphysema. While a majority [39, 102, 141] of pre- and post-mortem correlative studies would support this conclusion, not all do.[47] Also, this line of reasoning does not allow for other agents in the mines, such as toxic gases, in the pathogenesis of miners' emphysema.[20]

It is likely that deposition and clearance of dust will differ in normal and emphysematous lungs. This is supported by Heppleston's [50] observations in humans and by studies of experimental emphysema.[142, 143] It is not clear, however, whether retention of dust will be increased or decreased. Abnormal clearance as a result of tissue destruction in emphysema may account for increased amounts of coal dust observed in the liver and spleen of emphysematous coal workers.[144]

A proportion of miners' lungs at autopsy show a generalized form of emphysema (panacinar) with diffuse dust pigmentation (Figs. 17, 26). Histologically,

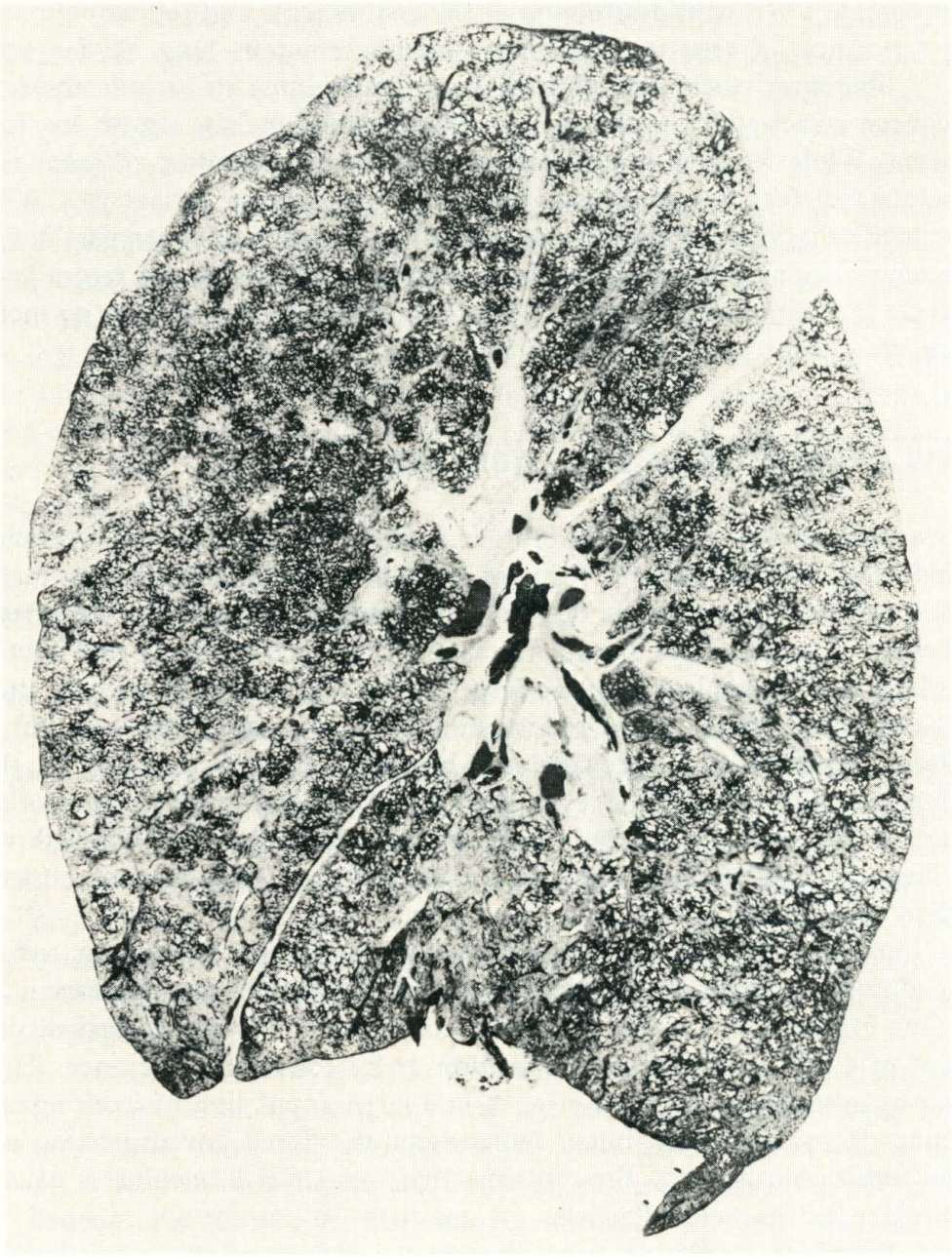


FIG. 26. Coal worker, no case details. Whole lung section shows diffuse dust deposition with moderate generalized (panacinar) emphysema. Discrete lesions of coal workers pneumoconiosis are not seen.

dust-laden macrophages are seen to be uniformly dispersed throughout the disrupted walls of the alveoli, and there may be mild interstitial fibrosis. Heppleston [50] has also drawn attention to this entity, and the German literature [145] refers to cases of Schwarzelocherlunge, literally "black hole" lung. We have found it to be a relatively common form of pneumoconiosis in a series of 700 miners autopsied in southern West Virginia from 1963 to 1972. In this condition, the pathognomonic features of CWP, i.e., the coal macule and focal emphysema, may be absent. It is therefore difficult, if not impossible, to determine whether the lesion represents

confluent simple CWP with destruction of the coal macule and redistribution of the dust or deposition of dust in a previously emphysematous lung. Ryder and colleagues [102] liberalized their definition of focal emphysema to include these cases. This has been criticized [146] on the grounds that it would include almost any form of emphysema. While we cannot accept Ryder's extended definition of focal emphysema, we do feel that this condition should be considered a variant of CWP until demonstrated otherwise. In view of the association between α_1-antitrypsin deficiency and panacinar emphysema, it would be of interest to determine the serum levels of this enzyme in this group of miners. Miners, in general, do not have an increased incidence of α_1-antitrypsin deficiency.[147]

CHRONIC BRONCHITIS IN COAL WORKERS

Bronchitis induced by organic and inorganic dusts generated in the workplace is called industrial bronchitis. This form of bronchitis is characterized by increased cough and sputum with evidence of mild flow limitation, which may be reversible. The majority of studies have shown a greater prevalence of cough and sputum in coal workers than in control groups. Early attempts to relate this to coal dust exposure were unsuccessful. More recent studies have shown a positive but small effect of dust exposure on the prevalence of bronchitis (reviewed in Ref. 8), though this is far less than the effect due to smoking. The condition in coal workers is characterized by mild decreases in flow at high lung volumes coupled with a normal lung capacity.[148] These changes are suggestive of large-airways obstruction rather than emphysema.

An interesting feature of industrial bronchitis is that increasing radiologic category of pneumoconiosis is not associated with a corresponding increase in bronchitis.[8] One explanation for this finding is that bronchitis protects against the development of CWP by decreasing deposition or by enhancing clearance. This hypothesis was investigated by Muir et al.[149] in a large population of working miners. They found no evidence that mucus hypersecretion offered any protection against simple pneumoconiosis. It is also possible that industrial bronchitis is caused by nonrespirable dust particles. Particles greater than 10 μm are not retained by the lungs and, therefore, would not contribute to the radiologic category of pneumoconiosis. Perhaps the most likely explanation for the lack of correlation between the radiologic category of CWP and industrial bronchitis is that cumulative exposure to coal dust is not necessary for the development of this disease.

Unfortunately, the morphologic correlates of industrial bronchitis have not been studied. It is not known whether the histology of industrial bronchitis is the same as chronic bronchitis. The pathology of chronic bronchitis involves hyperplasia of the goblet cells and hypertrophy and hyperplasia of the bronchial mucus glands. The airway basement membrane is frequently thickened, and the lamina propria may be edematous and infiltrated by lymphocytes, plasma cells, and occasional polymorphonuclear leukocytes. The severity of chronic bronchitis can be quantitated by the use of indices that measure the ratio of goblet cells to ciliated epithelial cells, the relative size of mucous glands (Reid index), and the relative

diameter of the airway lumen.[150] Post-mortem studies of coal miners have thus far been unable to demonstrate a relationship between dust exposure and chronic bronchitis.[150, 151] Ryder et al.[151] studied a population of 247 coal miners and ex-miners from Wales and compared them to an age- and sex-matched control group from the same area. They could find no significant difference in Reid indices between the two groups. In addition, the Reid index did not correlate with the forced expiratory volume in one second or with the radiographic category of either simple or complicated pneumoconiosis. Unfortunately, this study was not controlled for smoking. McKenzie and colleagues [150] examined the lungs of 136 autopsied Australian coal miners and showed a positive correlation between a clinical history of chronic bronchitis and the Reid index. However, when factors such as age and smoking were taken into account no clear relationship between occupational exposure and the Reid index or wall internal to cartilage/lumen radius ratio could be demonstrated.

PULMONARY VASCULAR LESIONS IN COAL WORKERS

Vascular abnormalities are common in the lungs of coal workers. It is therefore important to distinguish abnormalities related to occupation from those associated with aging, smoking, and other conditions.[43] Vascular abnormalities which can be directly related to CWP lesions are found in the coal macules and nodules and in PMF. It has been shown that the thickness of the small pulmonary arterial wall increases as the vessel traverses the coal macule.[43] The lesion is specific for the macule and appears to be due to hypertrophy of the arterial media. The functional significance of the lesion is unknown but is probably slight in view of the fact that none of the 10 cases studied showed a significant degree of right ventricular hypertrophy.

The vascular lesions observed in the nodules and in PMF are identical. They primarily involve the small pulmonary arteries, but pulmonary veins and bronchial arteries are also affected. The affected vessels show an arteritis involving all layers of the wall. The media is progressively replaced by fibrous tissue, sometimes in segmental fashion and endarteritis obliterans and thrombosis may lead to complete occlusion (Fig. 18). A prominent feature is the presence of numerous pigmented histiocytes within the walls of affected vessels (Fig. 27). Immunoglobulins and RF have been observed in vessels showing inflammatory changes.[128]

COR PULMONALE

The incidence of cor pulmonale in miners with PMF is higher than in those with simple CWP [47, 152-156] and is a common cause of death in miners with complicated CWP.[155] The mechanism whereby cor pulmonale is produced in PMF has been the subject of controversy. It could result from bronchial obstruction, obliteration of the vascular bed, or the development of shunts between the pulmonary arteries and bronchial artery. There is clinical evidence to support the first suggestion, as chronic

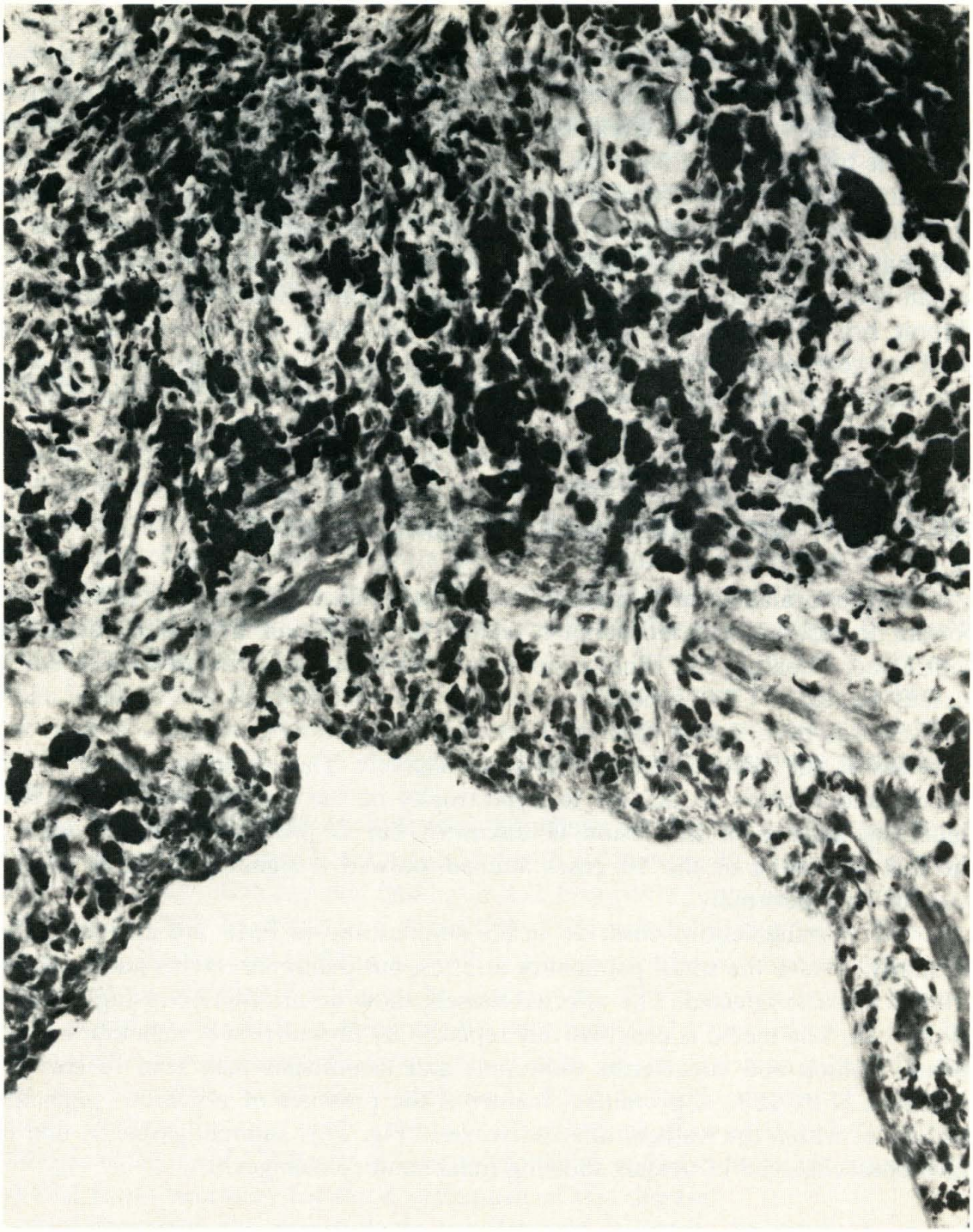


FIG. 27. Edge of pulmonary vein within progressive massive fibrosis. The vessel wall is infiltrated by chronic inflammatory cells, including numerous dust-containing macrophages. These latter extend to the intimal border. Numerous budding capillaries are present. H&E. ×390.

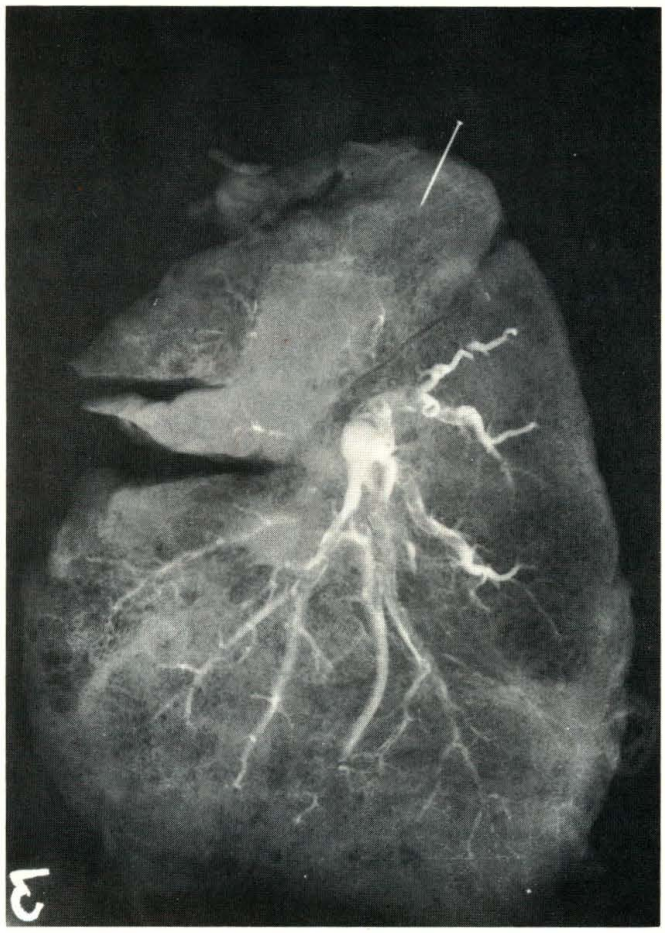


FIG. 28. A 78-year-old coal miner, worked 39 years underground, smoked a pack of cigarettes per day. Whole lung section showed macules, nodules, and progressive massive fibrosis with mild focal and scar emphysema. Post-mortem pulmonary arteriogram shows increased tortuosity of the vessels with decreased filling in areas of massive fibrosis (PMF). (Some of the filling defect may be due to ante-mortem thrombus.)

airway obstruction commonly accompanies PMF.[102, 155] Autopsy studies, on the other hand, suggest that obliterative vascular changes play a major role in the development of cor pulmonale.[156] The changes would have to be extensive, however, as it has been estimated that more than one-half of the vascular bed needs to be destroyed to produce obstructive pulmonary hypertension.[157] Figure 28 shows a post-mortem pulmonary arteriogram from a case of PMF with cor pulmonale. The great loss of pulmonary vasculature can be seen when compared to a normal arteriogram (Fig. 29). These findings are reflected in the clinical studies of Seaton et al.[158] They performed lung perfusion scans on 37 miners and exminers and showed that in all 14 with complicated pneumoconiosis and in 2 out of 3 with category 3 simple pneumoconiosis, there were avascular zones in relation to the conglomerate masses and nodules of CWP. They concluded that their findings were in remarkable agreement with the pathologic studies.

The final possibility is that shunts develop between pulmonary and bronchial arteries within the areas of fibrosis. Such lesions are known to occur within the fibrous tissue of bronchiectatic lungs and are associated with pulmonary hypertension.[159] Shunts have not been systematically searched for in PMF, but are less likely to occur in view of the destructive nature of the lesions.

Clinical cor pulmonale is rare in simple CWP unless there is also chronic airway obstruction.[8, 96, 152, 160] However, mild but statistically significant increases in

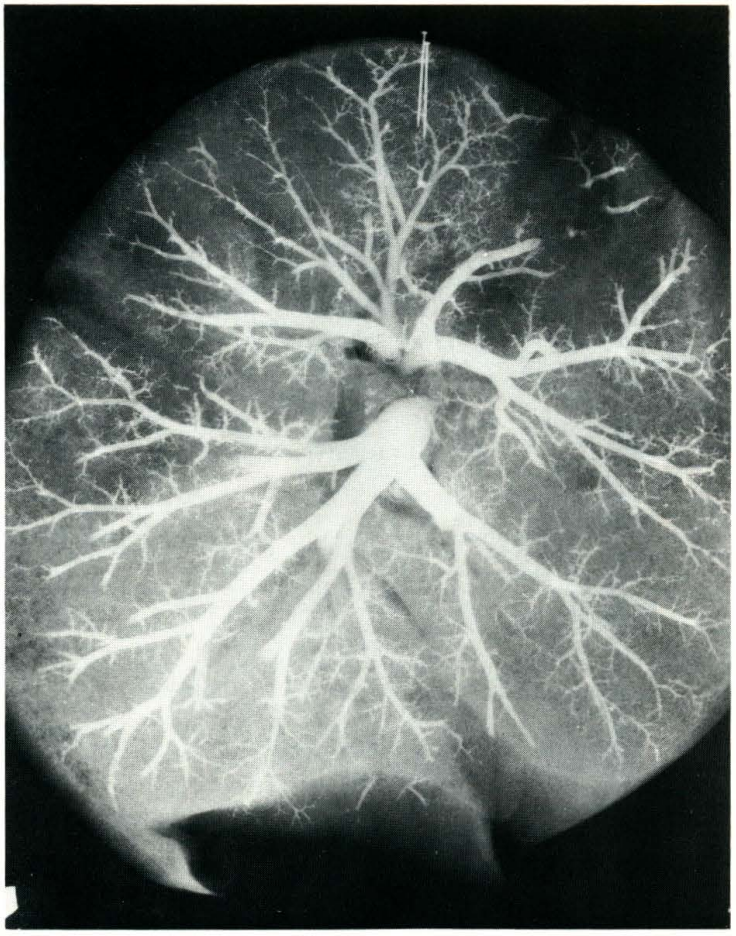


Fig. 29. A 45-year-old miner, worked in coal mines for 26 years, smoked a pack of cigarettes per day. Whole lung section showed mild macular CWP. The post-mortem pulmonary arteriogram appears normal.

pulmonary arterial pressure have been recorded at rest and on exercise in miners with simple CWP who do not have ventilatory disturbance.[96, 160, 161] These changes could result from reduction or loss of distensibility of the vascular bed, abnormalities of diffusion, or derangements in the ratio of ventilation to perfusion. Their anatomic basis may lie in the perivascular mantles of coal dust [161] or in the hypertrophic changes in the small pulmonary arteries as they traverse the coal macule.[43] There is no evidence that these minor abnormalities produce any noticeable impairment in the normal activities of work or daily living.

Autopsy studies in Great Britain have likewise failed to show an association between simple CWP and cor pulmonale.[51, 153, 154] In the United States, a high incidence of "cor pulmonale" has been observed in autopsied Appalachian coal workers with simple CWP.[152, 161, 162] The discrepancies between the studies in the United Kingdom and the United States probably reflect differences in diagnostic criteria. In the U.S. studies, cor pulmonale was defined in terms of right ventricular mass or right ventricular thickness. These measurements do not necessarily correlate with the right heart failure and dilatation necessary for a (clinical) diagnosis of cor pulmonale. To avoid confusion, we would prefer anatomic measurements not be used as synonyms for cor pulmonale.

The severity of right ventricular hypertrophy in the Appalachian miners correlated with the extent of emphysema, chronic bronchitis, and rank of coal but not

with the volume of the dust macules and nodules.[6, 152] These findings suggest that alveolar hypoxia secondary to chronic bronchitis and emphysema is more important than the lesions of simple CWP in producing right ventricular hypertrophy.

In summary there appears to be no doubt that cor pulmonale is a common complication of PMF. However, there is little or no evidence that simple CWP, *per se,* can cause cor pulmonale. The significance of the pulmonary arterial lesion in the coal macule and the slightly raised pulmonary arterial pressures recorded in simple CWP have yet to be determined.

LUNG CANCER

Whether exposure to coal mine dust increases the chances of developing carcinoma of the lung is a matter of considerable importance which has not been adequately resolved. There are many reasons for suspecting the environment of the coal mines may influence the incidence of lung cancer. Coal mine dust is a complex substance containing organic carcinogens such as the polycyclic aromatic hydrocarbons (PAH) [18] and trace amounts of metals, of which beryllium, cadmium, chromium, cobalt, lead, manganese, and nickel are carcinogenic in some mammalian species.[163]

Organic procarcinogens such as the PAHs require metabolism into an active form by the microsomal mixed-function oxidative enzyme system.[164] Two of the metals mentioned above, lead and cadmium, are able to inhibit this system and could, in theory, protect the lungs from the effects of the organic carcinogens.[165] Synergism between carcinogens and coal dust similar to that observed between asbestos and tobacco smoke is also possible.[166] The increasing use of diesel equipment in the mines raises the possibility of carcinogens being passively transported into the lungs adsorbed to coal dust and diesel particulates.[84]

The complexity of the problem from a theoretical standpoint makes the epidemiologic and pathologic data all the more important. The literature on the subject is somewhat contradictory and needs to be interpreted with caution. There are many difficulties in determining the true incidence of lung cancer in coal workers. In large studies, wide variations in incidence between different mines could counterevidence the findings. In small studies, regional variations in the incidence of lung cancer in nonminers [167] could cause bias unless a control population from the same region is used. The influence of smoking on lung cancer rates needs to be taken into account. Cigarette-smoking miners have an eightfold excess of lung cancer deaths when compared with nonsmoking miners.[168] The majority of studies we have reviewed suffer one or more of these limitations.

Several mortality studies based on death certificates and necropsy data have been published on U.S. and U.K. miners. The majority,[169-174] but not all,[175-178] show a decreased prevalence of lung cancer in coal workers. In 1947, Kennaway and Kennaway [172] published standard mortality ratios (SMR) for lung cancer by occupational group within the mines and found a considerable deficit for every category. The overall SMR for lung cancer was 59. In a later study they found a higher incidence of lung cancer in face workers.[179] James [180] reviewed 1,827 autopsies on

miners and 1,531 autopsies on nonminers and found the prevalence of carcinoma of the lung to be similar for the nonminers and the 967 miners with simple CWP. There was a significant deficit of lung cancer in the 860 miners with PMF, which led James to speculate that early death from pneumoconiosis was the factor responsible for the low incidence. Doll [181] attempted to correct for this factor by calculating a cause-specific SMR adjusted for deaths from other causes; he still found a significant reduction in overall mortality from lung cancer. A more recent study [174] based on autopsy data on 1,003 Lancashire coal miners has confirmed the low incidence of lung cancer in miners with PMF. Early death from pneumoconiosis was not a factor in this study, as the mean age at death was 72 years, which is slightly above the national average. The low incidence of lung cancer associated with PMF is unexpected, as lung scars in other circumstances are associated with an increased risk of cancer.[182]

The first mortality study of U.S. coal workers was based on the general occupational mortality for the year 1950 and was conducted by the U.S. Public Health Service.[176] The SMR for lung cancer in coal workers was 192. A later study based on a smaller population in the Beckley area of West Virginia confirmed this increase, though the SMR at 110.9 was lower.[173] Two mortality studies on a cohort of 3,726 Appalachian miners have been published.[169, 170] SMRs were computed using the entire U.S. population as a basis for comparison. The low SMR of 67 for lung cancer appeared to confirm the British findings. These were the first studies to take smoking into account and showed the expected excess of deaths from lung cancer in miners who smoke. A recent mortality study based on a cohort of 23,233 miners covered by the United Mine Workers Health and Retirement funds showed a slight overall excess mortality from lung cancer (SMR 112.5).[178] Examination of the raw data shows that this excess is largely derived from a few districts showing a high prevalence of lung cancer. Similar marked regional variations in the prevalence of lung cancer have been demonstrated in the English coal fields.[167] The SMR for lung cancer ranged from 63.2 in Durham to 147.0 in the northwest region.

Abraham [183] found 104 cases of primary lung cancer in the first 1,300 cases submitted to the National Coal Workers' Autopsy Study (NCWAS). Details of the cases are shown in Table 2. The expected excess of deaths of miners who smoked was confirmed. The data also showed the nonsmoking miner with lung cancer had worked for a significantly greater length of time underground when compared to the nonsmoking miner without lung cancer. This difference could not be explained on the basis of age. Firm conclusions cannot be drawn from this study, since the number of nonsmoking miners with lung cancer was small. It is currently being repeated with larger groups of miners.

An experimental study linking coal dust to lung cancer has been published by Martin.[16] Rats exposed to coal dust or a mixture of coal dust with 10 percent quartz showed lung tumors in 10 and 44 percent, respectively, after 24 months. The tumors were either adenocarcinomas or epidermoid tumors of low-grade malignancy. Tumors were not observed in control animals.

It is apparent from this review that no clear-cut answer to the problem of lung cancer in coal workers is possible at the present time. Future epidemiologic research should attempt to identify factors (e.g., radiation) associated with the mines

TABLE 2. Lung Cancer in U.S. National Coal Workers' Autopsy Study

Case Parameters	Smokers		Ex-Smokers		Never Smoked	
	Lung Cancer	Others	Lung Cancer	Others	Lung Cancer	Others
Number	30	380	64 †	444	10 †	352
Age at death *	65.7 ± 10.1	58.8 ± 10.1 †	64.1 ± 9.4	64.2 ± 9.9	71.2 ± 8.05	69.7 ± 11.63
Smoking history * (pack-years)	36.8 ± 24.1	27.5 ± 19.7 ‡	24.9 ± 15.4	19.9 ± 16.9 ‡	0	0
Years in underground job *	30.4 ± 15.6	26.8 ± 12.1	29.2 ± 14.4	28.5 ± 13.2	40.0 ± 8.98	29.7 ± 13.31 ‡

* Mean ± SD.
† $p < 0.01$.
‡ $0.01 < p < 0.05$.
From JL Abraham: The Lung, IAP Monograph No. 19, 1978. © 1978, U.S. Canadian Division of the IAP. Courtesy of the Williams & Wilkins Co.

or regions where there is a high incidence of lung cancer. Pathologic studies need to examine the distribution of lung cancer by histologic type between coal workers and non-coal-workers and determine the proportion of cancers related to scars.

CORRELATIVE STUDIES OF CWP

CWP is an unusual disease in that it can be diagnosed in any one of three distinct ways: by radiology, by pathology, and clinically. The radiologic and pathologic diagnoses primarily reflect the lung's dust content and its fibrous tissue response, whereas the clinical diagnosis is related more to the emphysema, chronic bronchitis, and pulmonary vascular abnormalities. Hence correlation between radiologic and pathologic findings in CWP is fairly good, whereas the correlation between these two and functional impairment (except in cases with PMF) is poor.[96, 184] These discrepancies have resulted in a polarization of medical opinion along differing and often radically opposed lines concerning the significance of simple CWP. Ideally, each diagnostic system should be directly translatable into the terms of the others. This is difficult for several reasons. First, there is no agreement as to what proportion of the bronchitis and emphysema seen in coal workers can be attributed to occupation; second, bronchitis, emphysema, and pulmonary vascular disease are difficult, if not impossible, to diagnose radiologically; third, the structural abnormalities of centriacinar emphysema (including focal) have not been firmly related to physiologic abnormality [184]; and fourth, the pathology of industrial bronchitis has yet to be described.[43]

The first attempt to correlate the radiologic and pathologic features of CWP was made by Gough et al. in 1949.[42] They studied 76 cases and made side-by-side comparisons of chest roentgenograms and whole lung sections. They concluded there was good correspondence between the number of opacities seen in the roentgenograms and the number of coal dust nodules seen in the lungs. Caplan [141] studied whole lung sections on 238 South Wales coal workers and compared these to the chest roentgenograms taken not more than 2 years before death. There was a fairly good correlation between the radiologic category and the number and character of dust foci in the lungs at necropsy. Rivers et al.[39] determined the total dust, coal, and mineral in a series of 45 lungs and compared these to the radiologic category of pneumoconiosis. A good correlation was found between total dust content of the lungs and radiologic category; however, the mineral component of the dust contributed nine times more to the radiographic density than did the coal dust component. This was explained on the basis of differing x-ray absorption characteristics between the coal and mineral constituents of the dust. They also concluded that the total dust content of the lungs bore a more direct relationship to the radiologic category than the tissue (fibrous) reaction to the dust. This contrasts with silicosis, where it has been shown that fibrous tissue reaction contributes more to the radiologic appearances than does the dust.[185]

Rossiter et al.[79] followed up the work of Rivers et al.[39] and extended it to include 88 lungs from a wider range of coal fields. Good to fair correlations were found between radiologic score and the iron content of the lung, total dust, coal

dust, years underground, collagen grading, mineral content, silica content, age at death, and focal emphysema in that order. There was no correlation between radiologic score and the degree of generalized emphysema. Later, Rossiter [80] investigated the relationship between radiologic category of simple CWP and dust content in a group of 221 miners. In this series, whole lung and histologic sections were not assessed. The average radiologic scores based on 11 independent readings correlated well with the coal, mineral, quartz, and iron content of the lungs. There was a small, but significant, residual relation of radiologic score to years in coal mining. Films showing larger nodular opacities were read in a higher category than would have been expected from the amount of dust in the lungs. This suggests that some factor, perhaps tissue reaction, in addition to dust contributes to this type of opacity. Films of poor technique tended to be read in the middle categories, irrespective of the dust content of the lungs.

To our knowledge only one comparable correlative study has been made on U.S. coal workers. Naeye and Dellinger [186] compared radiologic category of pneumoconiosis with lung pathology in a series of 77 coal workers. The roentgenograms were read by a panel of five experienced radiologists using the UICC/Cincinnati classification system. A good correlation was found between category of pneumoconiosis, volume of dust macules and nodules, and the silica and collagen content (determined morphometrically) of nodules and macules. However, there was poor roentgenographic recognition of emphysema and right ventricular hypertrophy—the two disorders which appear to be most closely related to disability.

A view commonly expressed is that emphysema tends to obscure the radiologic features of CWP (reviewed in Ref. 101). If this were true, a miner with emphysema and nodular lesions would be expected to have a lower radiologic category of pneumoconiosis than he would have had in the absence of the emphysema. The physics of radiology do not support this hypothesis,[101] and in fact, correlative studies [79, 141] have shown the opposite is more likely to be true, i.e., that emphysema actually increases the radiologic category of pneumoconiosis. A radiologic feature which may be directly attributable to emphysema has been recently demonstated by Lyons et al.[187] They showed that irregular opacities on the roentgenograms were highly correlated with the extent of post-mortem emphysema and antemortem ventilatory impairment, whereas the purely rounded opacities were not so correlated. This is the first study to show a direct relationship between certain radiologic, pathologic, and physiologic aspects of CWP.

Although simple CWP is associated with mild but definite functional abnormalities,[8, 155] it has not been possible to relate these changes to the radiologic category (an index of profusion) of simple CWP.[101, 102, 188, 189] There is some evidence that the size [189] or type of opacity [187] may be related to specific functional abnormalities. These latter findings deserve much more attention than they have so far received. There is a good correlation between abnormalities on the chest roentgenogram and abnormalities in pulmonary function in PMF. Categories B and C complicated PMF are associated with a marked reduction in ventilatory function with low diffusing capacity, gas-exchange abnormalities, and pulmonary hypertension.[152]

Finally, very few studies have attempted to relate physiologic findings in CWP

to the lesions encountered at autopsy. The relationship between chronic bronchitis, emphysema, and cor pulmonale at autopsy with clinical findings have already been discussed under the respective subject headings and are reviewed by Lamb.[184] We are currently analyzing the clinical, pathologic, radiologic, smoking, and occupational data on a series of 700 underground coal workers. The results from this study should provide answers to some of the unresolved problems outlined above.

Correlative Studies Using Lyophilized Lungs

RADIOLOGIC. The relationship between radiologic opacities and the physical reality of a lesion has been investigated in plastic models [190] and in deconstructed human lungs.[191] Factors responsible for the radiologic appearances include the size, shape, and composition of the lesions; the background density of the lung; and the effects of summation and emphysema. The major constituent of coal, carbon, has an atomic number which is similar to the average atomic number of tissue constituents. It is not surprising, therefore, that the iron and mineral components of coal mine dust contribute more to the radiologic score than does the carboniferous component.[39, 80] The size of the lesion is important. Spherical lesions less than 6 mm in diameter are difficult to resolve by conventional radiologic techniques [191]; for this reason it is unlikely that individual macules will appear on a roentgenogram.

In order to understand these relationships better, a procedure for freeze-drying human lungs has been developed at the Appalachian Laboratory for Occupational Safety and Health.[192] Existing methods for preserving lungs for correlative studies, such as wet and dry fixation and wet and dry ashing, result in either contamination of the specimen, poor x-ray contrast, or destruction of the tissue. Freeze-drying does not have these disadvantages and thus allows for the detailed correlation of pathologic, radiologic, and mineralogic features of the disease. The apparatus we use for freeze-drying coal workers' lungs is shown in Fig. 30. The

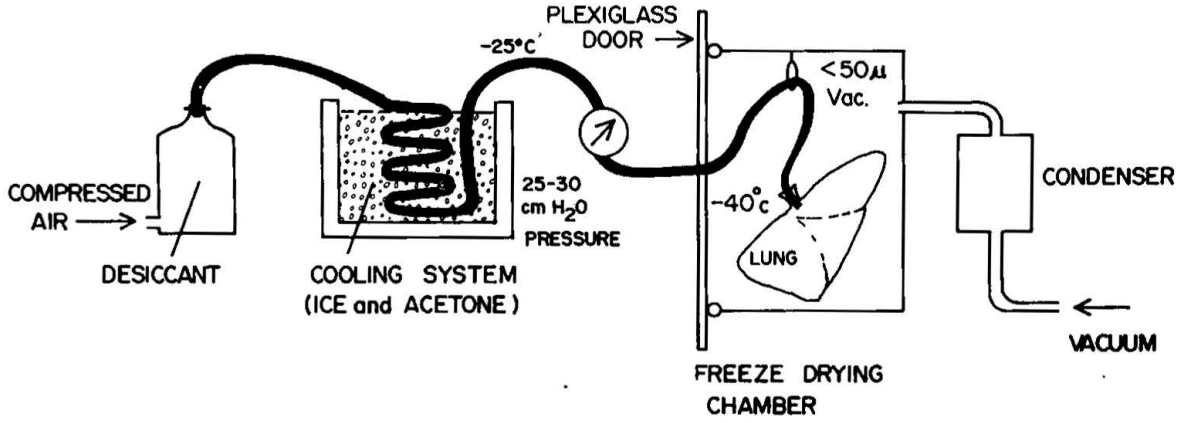


FIG. 30. Diagram of apparatus designed for freeze-drying human lungs. The unfixed lung is cannulated, inflated with cooled air, and placed in the freeze-drying chamber. When the lung is frozen, the cannula is removed, the chamber sealed, and a vacuum applied. Dehydration takes two to three weeks.

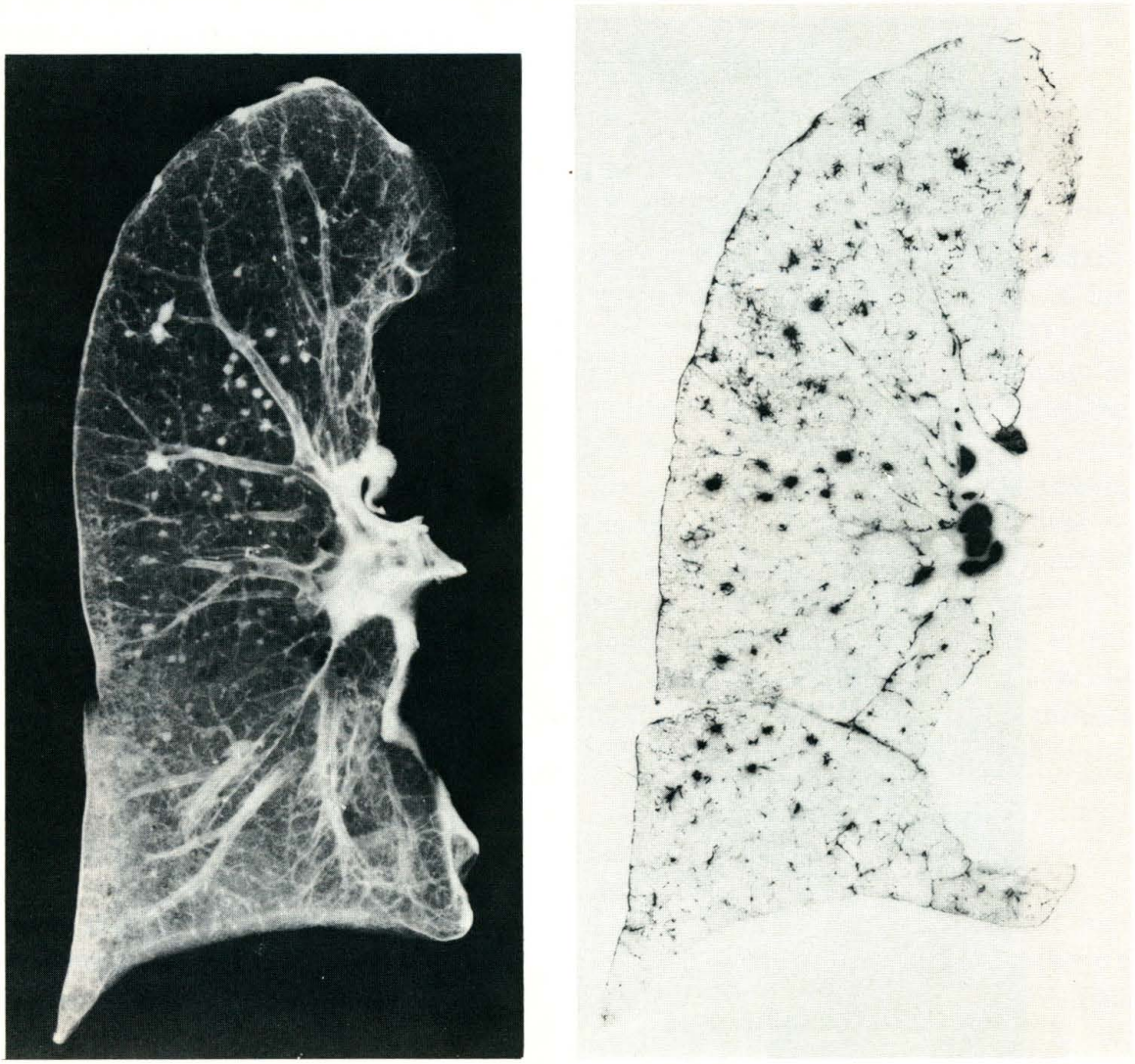


FIG. 31. Left. Roentgenogram of 1-cm-thick slice of lyophilized (freeze-dried) lung. The round opacities correspond with micronodular lesions. Macular lesions are not resolved. **Right.** Whole lung section prepared from same slice showing micronodules and macules.

finished specimen has the consistency of polystyrene foam and can be radiographed, sliced to produce whole lung sections, and processed for light microscopy and chemical analysis. Examples of coal workers' lungs processed by this method are shown in Figs. 31 and 32. These cases illustrate that individual macules are insufficiently x-ray opaque to be resolved, whereas the larger fibrotic nodules are readily apparant. Studies designed to correlate the elemental composition of the lesions with the radiologic appearances using x-ray fluorescence and energy-dispersive x-ray analysis are in progress.

MAGNETOMETRY. Small quantities of ferrimagnetic material can be accurately measured in the lungs of living subjects using the recently developed technique of magnetopneumography.[193] The technique involves applying a uniform magnetic field across the lungs and then measuring the remnant magnetic field using a sensi-

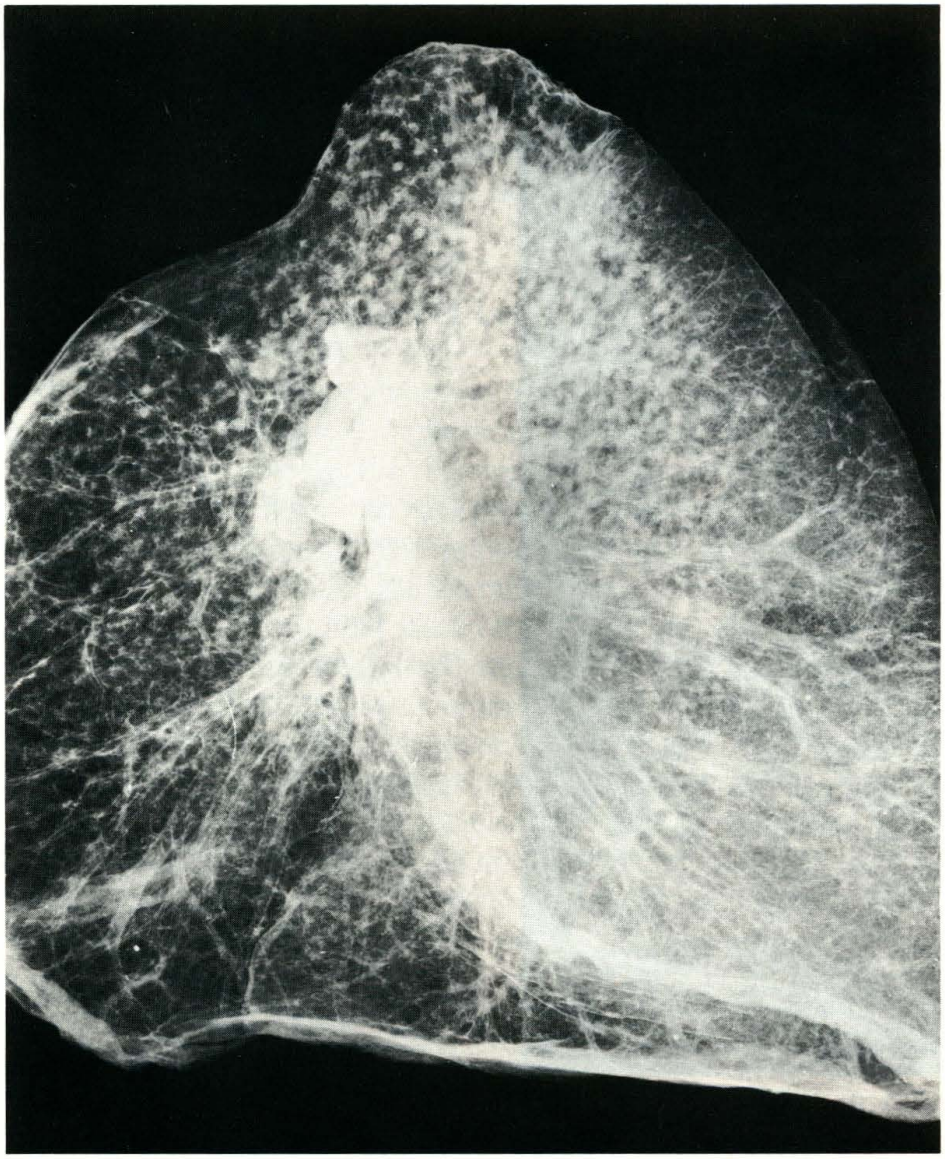


FIG. 32. Roentgenogram of whole lyophilized (freeze-dried) lung from coal miner. The profusion of nodular opacities is greatest in the upper zone. Superimposition of small nodules gives the impression of a single large lesion in this area.

tive SQUID or fluxgate magnetometer. The resultant field is proportional to the amount of ferrimagnetic material present. It has proven useful in studies of iron and steel workers, welders, and asbestos workers, in whom the concentration of ferrimagnetic material in the inhaled dust is high.[193] The major advantages of this technique are that it is safe, noninvasive, and quantitative. The disadvantages are that it will only measure the ferrimagnetic component of the dust and that it does not give information concerning tissue response.

The ferrimagnetic component of coal mine dust is low and is largely derived from oxides of iron. Studies in living coal miners, however, have shown the technique is sensitive enough to detect these small amounts.[194] We are currently applying the technique to freeze-dried lungs from groups of miners and nonminers in order to determine if there is a correlation between magnetometry, radiology, and

the dust content of the lungs. The theoretical aspects of magnetometric dust assessment in lung models and freeze-dried coal workers' lungs have been published.[195]

EXTRAPULMONARY PATHOLOGY

Coal dust is frequently encountered in extrapulmonary sites in coal workers. The abdominal para-aortic lymph nodes in coal miners are usually enlarged and heavily pigmented. They may show typical silicotic nodules. Coal dust is also seen in the liver and spleen in about 20 percent of miners (Green et al., unpublished). The pigment lies in the connective tissues of the portal tracts in the liver and encircles the arterioles in the spleen (Fig. 33). The pigment could be derived from either the gastrointestinal tract or the lungs. It appears to have little pathologic effect. An unusual case of hepatic cirrhosis was described by Welch in 1891.[144] The patient, who died of carcinomatosis, showed massive deposits of coal dust in his liver in association with bands and nodules of dense fibrous tissue. Welch was so impressed by this lesion that he termed it "cirrhosis hepatis anthracotica." We have not observed this lesion, though we have occasionally observed silicotic nodules in the spleens of coal miners. The possible role of extrapulmonary coal dust in diseases in coal workers deserves more attention, especially in view of the fact that a distinct form of nephropathy has been observed in patients with pulmonary silicosis.[196]

CANCER OF THE STOMACH

While there is no clear evidence for an association between lung cancer and coal mining, there is a consensus that coal miners in both Europe and the United States have a higher than expected mortality from carcinoma of the stomach.[170, 173, 175, 178] This is a specific phenomenon, as mortality from other forms of malignancy is not increased. No satisfactory explanation has been advanced. Matolo et al.[197] have suggested that carcinoma of the stomach was more common in miners with categories 1 and 2 than category 3 pneumoconiosis. They concluded their findings do not support the dust hypothesis. This line of reasoning can be criticized on the grounds that radiologic category is an index of retained dust in the respirable range and does not necessarily reflect exposure to the larger particles. The larger particles are more likely to be cleared by the upper airways and swallowed than the smaller particles. Much of the dust entering the stomach from this source will be within alveolar macrophages, cells that may be capable of metabolizing the procarcinogens in coal into their active forms.

A factor which could be of importance in the etiology of stomach cancer in miners is the practice of tobacco chewing. Coal miners smoke about the same numbers of cigarettes as nonminers but are not permitted to smoke underground.[98] Consequently, tobacco chewing is more common in mining than in other industries. The majority of the carcinogens associated with tobacco smoke are formed during combustion. A recent report, however, has shown that unburned tobacco contains *N*-nitrosonornicotine, a potential oncogen, in concentrations ranging from 1.9 to 88.6 parts per million.[198] This is the highest value yet reported for an environmental nitrosamine.

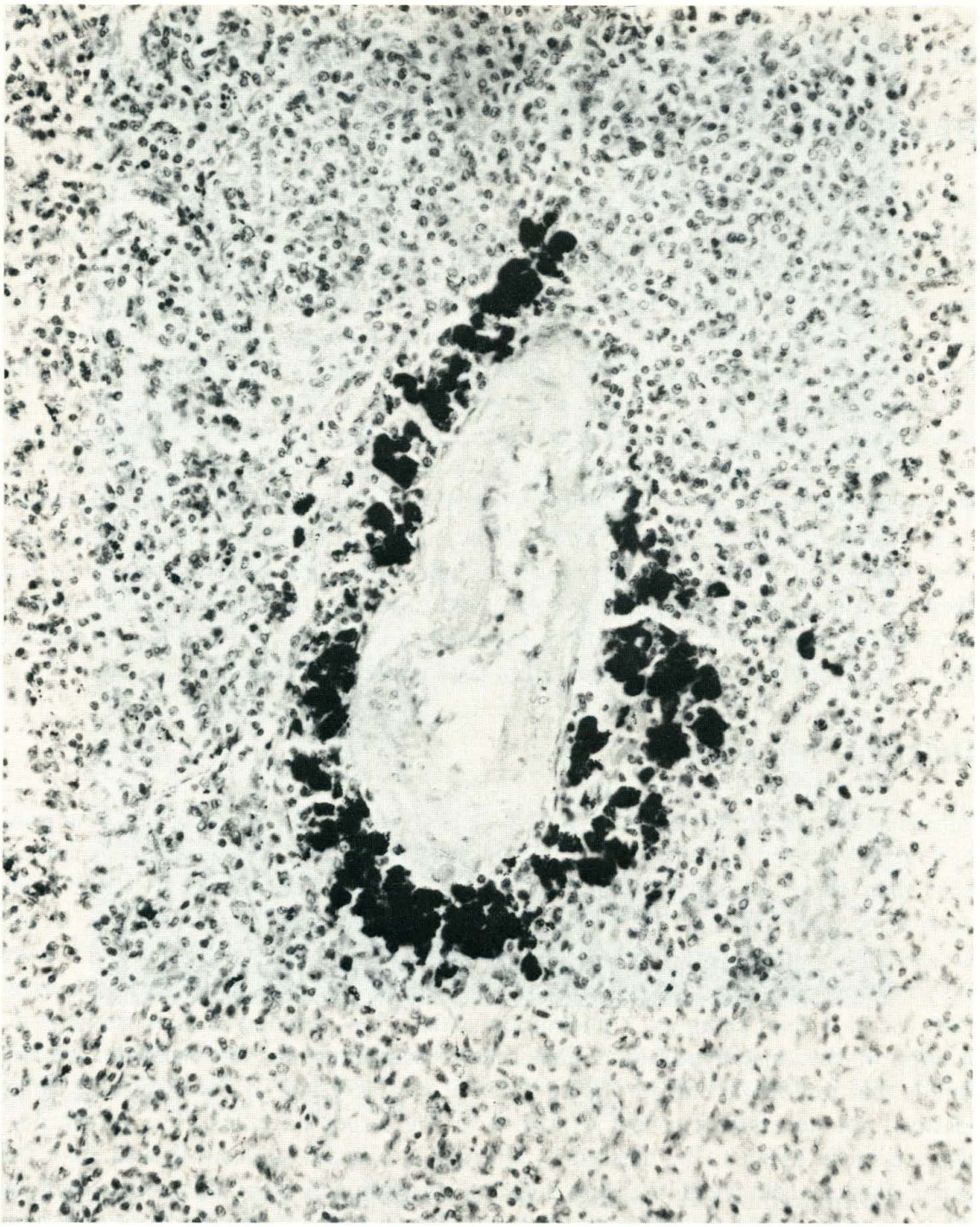


FIG. 33. Section of spleen from a retired coal miner. Coal dust is seen within macrophages adjacent to a small arteriole. This distribution is characteristic. H&E. ×390.

NATIONAL COAL WORKERS' AUTOPSY STUDY

A nationwide autopsy program for underground coal miners was initiated under the Federal Coal Mine Health and Safety Act of 1969.[5] The purpose of the program differs from autopsy programs in other countries in that submission is voluntary and is not confined to cases receiving compensation.[151] In the NCWAS, the autopsy is

TABLE 3. U.S. National Coal Workers' Autopsy Study Cases by State

State	Number	Percent
Pennsylvania	594	47
West Virginia	350	28
Illinois	71	6
Ohio	50	4
Kentucky	49	4
Virginia	41	3
Wyoming	26	2
Colorado	23	2
Utah	9	1
New Mexico	7	1
Kansas, Michigan	6	0.5
Tennessee	5	0.4
Oklahoma, Missouri	4	0.3
Indiana, New Jersey	3	0.23
New York, Washington, Washington D.C.	2	0.16
Arizona, Connecticut, Florida, Georgia, Oregon, Texas	1	0.08

From JL Abraham: The Lung, IAP Monograph No. 19, 1978. © 1978, U.S. Canadian Division of the IAP. Courtesy of the Williams & Wilkins Co.

requested by the surviving relatives and paid for by the federal government. The results are confidential. Requirements for submission to the NCWAS have been published [100] or can be obtained directly from NIOSH.*

An acceptable case includes an autopsy report, lung blocks, slides, and a personal history form. The pathologist is also encouraged to submit a recent clinical roentgenogram. The study suffers from the epidemiologic limitation that the sample is uncontrolled. This may not be a major drawback, however, as the NCWAS population is similar to the general working miner population with regard to geographic distribution, occupation within the mines, and smoking history. Since its inception in 1972, 2,400 cases have been included from 26 states. The basic data on the first 1,299 cases are shown in Tables 3 to 6. Pneumoconiosis was determined to be the underlying cause of death by the pathologist in 4 percent of cases. This figure may not accurately reflect the true incidence, however, as the sample is biased toward miners who were not receiving benefits during life and may therefore contain fewer cases of the severe forms of disease.

The data in the NCWAS have been used to compare death certificate diagnoses with autopsy diagnoses. This allows an estimate of biases in counts of deaths due to specific diseases in coal miner mortality studies when only reports of causes of death from death certificates are used. Table 7 shows that from 10 to 30 percent and more of autopsy diagnoses of underlying causes of death were omitted from death certificates. A larger study by Heasman and Lipworth [99] in a nonmining population found similar major discrepancies. As almost all mortality statistics are based on death certificate data, these findings are of considerable importance. The inaccuracy of death certificate reporting was one of the reasons why the anatomic

* NIOSH, 944 Chestnut Ridge Road, Morgantown, West Virginia 26505.

TABLE 4. Distribution of Autopsies in U.S. National Coal Workers' Autopsy Study

Type of Death	Number	Type of Autopsy		
		Complete	Brain Excluded	Heart and Lungs Only
Hospital	297 (22.92%)	131 (10.11%)	143 (11.03%)	23 (1.77%)
Dead on Arrival	103 (7.94%)	21 (1.62%)	35 (2.70%)	47 (3.63%)
Embalmed	896 (69.14%)	102 (7.87%)	693 (53.47%)	101 (7.79%)
Total	1296	254 (19.60%)	871 (67.21%)	171 (13.19%)

From JL Abraham: The Lung, IAP Monograph No. 19, 1978. © 1978, U.S. Canadian Division of the IAP. Courtesy of the Williams & Wilkins Co.

TABLE 5. Smoking History in the U.S. National Coal Workers' Autopsy Study

Smoking Status	Number	Percent
Never smoked	334	25.7
Cigar or pipe only	31	2.4
Ex-smoker	509	39.2
Current smoker	394	30.3
Unknown status	31	2.2
Total	1299	100

From JL Abraham: The Lung, IAP Monograph No. 19, 1978. © 1978, U.S. Canadian Division of the IAP. Courtesy of the Williams & Wilkins Co.

TABLE 6. Mining History in the National Coal Workers' Autopsy Study

Years in Underground Mining	Number	Percent
0–10	136	11.68
11–20	217	18.64
21–30	284	24.40
31–40	323	27.75
41–50	174	14.95
51–61	30	2.58

TABLE 7. Specified Diagnoses Reported as Related to Death on Death Certificate and After Autopsy: 1299 Deaths of Coal Miners, U.S. 1970–74 *

Diagnoses ‡	Autopsy	Combinations of Classifications of Diagnoses †							
	Death Certificate	Primary	Primary	Primary	Contributing	Contributing	Contributing	No Report	No Report
	Number	Underlying	Contributing	No Report	Underlying	Contributing	No Report	Underlying	Contributing
		Coal Miners Deaths							
Respiratory tuberculosis	45	7	4	4	1	2	18	1	8
Malignant neoplasm									
Bronchus and lung	110	69	0	8	6	7	13	7	0
Digestive system	92	60	2	9	2	1	11	5	2
Arteriosclerosis, hypertensive heart disease, and myocardial infarction	992	330	48	45	127	89	309	25	19
Pulmonary embolism	143	7	20	10	6	24	67	1	8
Obstructive lung diseases	910	8	14	9	17	146	688	4	24
Pneumoconioses	1195	22	9	7	108	455	574	2	18
Ulcers, peptic	105	6	5	5	2	6	79	0	2
Cirrhosis, liver	81	21	5	3	2	10	32	2	6
Cerebrovascular disease	172	49	14	8	11	11	40	21	18

* Autopsies paid for and reports received by the Appalachian Laboratory for Occupational Safety and Health, NIOSH, CDC, U.S. DHEW, in their National Coal Workers' Autopsy Study (authorized in the Federal 1969 Coal Mine Health and Safety Act).

† Classified according to the Diagnostic Codes, ICDA, 8th Revision.

‡ Diagnoses reported at autopsy, with clinical summaries, were reviewed by J. L. Abraham, M.D., Formerly Chief, Pathology Section, ALOSH-NIOSH, who designated "Primary" and "Other" diagnoses related to each death; causes of death reported on each death certificate were coded and designated "Underlying" or "Other" according to rules of the ICDA, 8th revision.

Courtesy of Dr. C. E. Ortmeyer.

committee of the College of American Pathologists initiated a nationwide autopsy data bank in 1977.[200] When operational, this undertaking will provide a source of mortality statistics derived directly from autopsies. The data will be used to provide a better index of the true incidence of disease and as a sensitive way to monitor the nation's health.

TRENDS AND DEVELOPMENT

In the foreseeable future, coal is going to play an increasingly important role in supplying this country's energy. As a consequence there will be pressure to develop new techniques and more efficient methods for mining coal. These will present new health hazards in the industry. A trend already apparent is the increasing use of diesel equipment in the mines. The combined effects of diesel exhaust and coal mine dust on the respiratory system are virtually unknown. A recent NIOSH study has shown there are adverse short-term health effects associated with dieselized coal mines.[84] Coal miners exposed to diesel exhaust had a greater incidence of cough, phlegm, and decreased pulmonary function performance than did a carefully matched group of miners who were not exposed to diesel emissions. More serious health effects of combined exposure such as emphysema and bronchial carcinoma may not manifest for 20 or 30 years. Experimental studies designed to document the long-term health effects of coal dust and diesel emissions are in progress in a joint venture by NIOSH and the Environment Protection Agency.

Although there is evidence that dust control technology is reducing the incidence of CWP, the increased production of coal, new mining methods, and the development of coal-conversion technologies will undoubtedly lead to new forms of environmental disease.[201] The pathologist will play a leading role in the recognition of these entities.

ACKNOWLEDGMENT

We would like to thank Carol Hando for preparing the illustrations, Marilyn Gamble for secretarial assistance, and Molly Fredlock, V. Vallyathan, D. Gnepp, D. Pearson, J. L. Abraham, and L. Lapp for helpful suggestions in preparing the manuscript.

APPENDIX. UICC/Cincinnati Classification of Radiographic Appearances of Pneumoconioses

	Codes	Definitions
Small Opacities		The category of profusion is based on assessment of the concentration of opacities in the affected zones. The standard films define the mid categories.
Rounded profusion		
	0/– 0/0 0/1	Category 0—small rounded opacities absent or less profuse than in category 1.
	1/0 1/1 1/2	Category 1—small rounded opacities definitely present but relatively few in number.
	2/1 2/2 2/3	Category 2—small rounded opacities numerous. The normal lung markings are usually still visible.
	3/2 3/3 3/4	Category 3—small rounded opacities very numerous. The normal lung markings are partly or totally obscured.
Type	p q r	The nodules are classified according to the approximate diameter of the predominant opacities. p—rounded opacities up to about 1.5 mm diameter. q—rounded opacities exceeding about 1.5 mm and up to about 3 mm diameter. r—rounded opacities exceeding about 3 mm and up to about 10 mm diameter.
Extent	Lung zones	The zones in which the opacities are seen are recorded. Each lung is divided into thirds —upper, middle, lower zones. Thus a maximum of 6 zones can be affected.
Irregular profusion		The category of profusion is based on assessment of the concentration of opacities in the affected zones. The standard films define the midcategories.
	0/– 0/0 0/1	Category 0—small irregular opacities absent or less profuse than in category 1.
	1/0 1/1 1/2	Category 1—small irregular opacities definitely present but relatively few in number. The normal lung markings are usually visible.
	2/1 2/2 2/3	Category 2—small irregular opacities numerous. The normal lung markings are usually partly obscured.
	3/2 3/3 3/4	Category 3—small irregular opacities very numerous. The normal lung markings are usually totally obscured.

(Continued)

APPENDIX. UICC/Cincinnati Classification of Radiographic Appearances of Pneumoconioses (cont.)

	Codes	Definitions
Type	s t u	As the opacities are irregular, the dimensions used for rounded opacities cannot be used, but they can be roughly divided into three types. s—fine irregular or linear opacities. t—medium irregular opacities. u—coarse (blotchy) irregular opacities.
Extent	Lung zones	The zones in which the opacities are seen are recorded. Each lung is divided into thirds —upper, middle, lower zones—as for rounded opacities.
Large Opacities		
Size	A B C	Category A—an opacity with greatest diameter between 1 cm and 5 cm, or several such opacities the sum of whose greatest diameters does not exceed 5 cm. Category B—one or more opacities larger or more numerous than those in category A, whose combined area does not exceed one-third of the area of the right lung. Category C—one or more large opacities whose combined area exceeds one third of the area of the right lung.
Type	wd id	As well as the letter 'A,' 'B' or 'C,' the abbreviation 'wd' or 'id' should be used to indicate whether the opacities are well defined or ill defined.
Other features		
Pleural thickening		
Costophrenic angle	Right Left	Obliteration of the costophrenic angle is recorded separately from thickening over other sites. A lower limit standard film is provided. Grade 0—not present or less than grade 1. Grade 1—up to 5 mm thick and not exceeding one-half of the projection of one lateral chest wall. A lower limit standard film is provided. Grade 2—more than 5 mm thick and up to one-half of the projection of one lateral chest wall *or* up to 5 mm thick and exceeding one-half of the projection of one lateral chest wall. Grade 3—more than 5 mm thick and extending more than one-half of the projection of one lateral chest wall.
Other sites	1 2 3	

Diaphragm, ill-defined	Right Left	The lower limit is one-third of the affected hemidiaphragm. A lower limit standard film is provided.
Cardiac outline, ill-defined (shagginess)	1 2 3	Grade 0—up to one-third of the length of the left cardiac border or equivalent. Grade 1—above one-third and up to two-thirds of the length of the left cardiac border or equivalent. Grade 2—above two-thirds and up to the whole length of the left cardiac border or equivalent. Grade 3—more than the whole length of the left cardiac border or equivalent.
Pleural calcification Diaphragm Walls Other sites	1 2 3	Grade 0—no pleural calcification seen. Grade 1—one or more areas of pleural calcification, the sum of whose greatest diameters does not exceed 2 cm. Grade 2—one or more areas of pleural calcification, the sum of whose greatest diameters exceeds 2 cm but does not exceed 10 cm. Grade 3—one or more areas of pleural calcification, the sum of whose greatest diameters exceeds 10 cm.

Other symbols

Obligatory

- ca —suspect cancer of lung or pleura.
- co —abnormality of cardiac size or shape.
- cp —suspect cor pulmonale.
- es —eggshell calcificaton of hilar or mediastinal lymph nodes.
- tba —opacities suggestive of active clinically significant tuberculosis.
- od —other significant disease. This includes disease not related to dust exposure, e.g., surgical or traumatic damage to chest walls, bronchiectasis, etc.

Optional

- ax —coalescence of small rounded pneumoconiotic opacities.
- bu —bullae.
- cn —calcification in small parenchymal opacities.
- cv —cavity.
- di —marked distortion of the intra-thoracic organs.
- em —marked emphysema.
- hi —marked enlargement of hilar shadows.
- ho —honeycomb lung.
- k —Kerley (septal) lines.
- px —pneumothorax.
- rl —pneumoconiosis modified by rheumatoid process.
- tb —inactive tuberculosis.

Reproduced with permission from "UICC/Cincinnati classification of the radiographic appearance of the pneumoconioses." Chest 58:60, 1970.

REFERENCES

1. Committee on Industrial Pulmonary Disease, Medical Research Council: Gt Br Spec Rep Ser, 1942/43, p 243
2. Meiklejohn A: History of lung diseases of coal miners in Great Britain: Part III. Br J Ind Med 9:208, 1952
3. Klosterkotter W: In Staublungener Krankungen, Vol. Wiss. Forschungsberichte Darmstady, 1954
4. Lee OHK: Historical aspects. In Key MM, Kerr LE, Bundy M (eds): Pulmonary Reactions to Coal Dust. New York, Academic, 1971, p 3
5. Federal Coal Mine Health and Safety Act, Public Law 91–173, December 30, 1969
6. Naeye RL, Mahon JK, Dellinger WS: Rank of coal and coal workers' pneumoconiosis. Am Rev Resp Dis 103:350, 1971
7. Schlick DP, Fannick NL: Coal in the United States. In Key MM, Kerr LE, Bundy M (eds): Pulmonary Reactions to Coal Dust. New York, Academic, 1971, p 13
8. Morgan WKC, Lapp NL: Respiratory disease in coal miners. In Murray JF (ed): Lung Disease—State of the Art. New York, American Lung Assoc, 1977
9. Doyle HN: Dust Concentrations in the Mines, Proceedings of Symposium on Respirable Coal Mine Dust. Washington DC, Bureau of Mines Information, Circular No. 8458, 1969
10. Fairman RP, O'Brien RJ, Swecker S, et al.: Respiratory status of surface coal miners in the United States. Arch Environ Health 32:211, 1977
11. Jacobsen M, Rae S, Walton WH, Rogan JM: The relation between pneumoconiosis and dust exposure in British coal mines. In Walton WH (ed): Inhaled Particles III, Vol. 2. Surrey, England, Unwin, 1971, p 903
12. DeNee PB: Mine dust characterization using the scanning electron microscope. Am Ind Hyg Assoc J 33:645, 1972
13. Leiteritz H, Bauer D, Bruckmann E: Mineralogical characteristics of airborne dust in coal mines of Western Germany and their relations to pulmonary changes of coal hewers. In Walton WH (ed): Inhaled Particles III, Vol 2. Surrey, England, Unwin, 1971, p 729
14. Freedman RW, Sharkey AG Jr: Recent advances in the analysis of respirable coal dust for free silica, trace elements and organic constituents. Ann NY Acad Sci 200:7, 1972
15. Reisner MTR, Robock K: Results of epidemiological, mineralogical and cytotoxicological studies on the pathogenicity of coal mine dusts. In Walton WH (ed): Inhaled Particles IV, Vol 2. New York, Pergamon, 1975, p 703
16. Martin JC, Daniel H, LeBouffant L: Short and long term experimental study of the toxicity of coal mine dust and of some of its constituents. In Walton WH (ed): Inhaled Particles IV, Vol 1. New York, Pergamon, 1975, p 361
17. Christian RT, Nelson J: Coal: Response of cultured mammalian cells corresponds to the prevalence of coal workers' pneumoconiosis. Environ Res 15:232, 1978
18. Naeye RL: Black lung disease, the anthracotic pneumoconioses. Pathol Annu 8:349, 1973
19. Kibelstis JA: Medical Effects of Diesels Underground: Proceedings of the Symposium on the Use of Diesel-Powered Equipment in Underground Mining. Washington DC, Bureau of Mines, Circular 8666, 1975
20. Kennedy MCS: Nitrous fumes and coal-miners with emphysema. Ann Occup Hyg 15:285, 1972
21. Boren HG: Pulmonary response to inhaled carbon: A model of lung injury. Yale J Biol Med 40:364, 1968
22. Melandri C, Prodi V, Tarroni G, et al.: On the deposition of unipolarly charged

particles in the human respiratory tract. In Walton WH (ed): Inhaled Particles IV, Vol 1. New York, Pergamon, 1975, p 193
23. Albert RE, Lippmann M: Factors that influence dust retention in the pulmonary parenchyma. Ann NY Acad Sci 200:37, 1972
24. Love RG, Muir DCF, Sweetland KF: Aerosol deposition in the lungs of coal workers. In Walton WH (ed): Inhaled Particles III, Vol 1. Surrey, England, Unwin, 1971, p 181
25. Brain JD: Free cells in the lungs. Arch Intern Med 126:477, 1970
26. Gross P: Some aspects of pneumoconiosis. Pathol Annu 6:61, 1971
27. Lippmann M, Albert RE, Yeates DB, et al: Factors affecting tracheobronchial mucociliary transport. In Walton WH (ed): Inhaled Particles IV, Vol 1. New York, Pergamon, 1975, p 305
28. Ferin J, Leach LJ: The effects of selected air pollutants on clearance of titanic oxide particles from the lungs of rats. In Walton WH (ed): Inhaled Particles IV, Vol 1. New York, Pergamon, 1975, p 333
29. Strecker FJ: Tissue reactions in rat lungs after dust inhalation with special regard to bronchial dust elimination and to the penetration of dust into the lung interstices and lymphatic nodes. In Davis N (ed): Inhaled Particles and Vapors II. Oxford, Pergamon, 1967, p 141
30. Heppleston AG: The pathogenesis of simple pneumoconiosis in coal workers. J Pathol Bacteriol 67:51, 1954
31. Leak LV: Pulmonary lymphatics and their role in the removal of interstitial fluids and particulate matter. In Brain JD, Proctor DF, Reid LM (eds): Respiratory Defence Mechanisms, New York, Dekker, 1977, Part II, p 631
32. Sorokin SP, Brain JD: Pathways of clearance in mouse lungs exposed to iron oxide aerosols. Anat Rec 181:581, 1975
33. Spencer H: The pneumoconioses and other occupational lung diseases. In: Pathology of the Lung. New York, Macmillan, p 286, 1962
34. Weller W, Ulmer WT: Inhalation studies of coal-quartz dust mixture. Ann NY Acad Sci 200:142, 1972
35. Carlberg JR, Crabble JV, Limtiaca LP, et al: Total dust, coal, free silica, and trace metal concentrations in bituminous coal miners' lungs. Am Ind Hyg Assoc J 32:432, 1971
36. Lauweryns JM, Baert JH: The role of the pulmonary lymphatics in the defences of the diseased lung: Morphological and experimental studies of the transport mechanisms of intratracheally instilled particles. Ann NY Acad Sci 221:244, 1974
37. Heppleston AG: The disposal of dust in the lungs of silicotic rats. Am J Pathol 40:493, 1962
38. Gross P, McNerney JM, Babyak MA: Experimental silicosis: A quantitative study of dust mobilization. Am Ind Hyg Assoc J 23:379, 1962
39. Rivers D, Wise ME, King EJ, Nagelschmidt G: Dust content, radiology, and pathology in simple pneumoconiosis of coal workers. Br J Ind Med 17:87, 1960
40. King EJ, Zaidi S, Harrison CV, Nagelschmidt G: The tissue reaction in the lungs of rats after the inhalation of coal dust containing 2% quartz. Br J Ind Med 15:172, 1958
41. Heppleston AG: Essential lesion of pneumoconiosis in Welsh coal workers. J Pathol Bacteriol 59:453, 1947
42. Gough J, James WRL, Wentworth JE: A comparison of the radiological and pathological changes in coal workers pneumoconiosis. J Fac Radiol (London) 1:28, 1949
43. Kleinerman J, Green F, Lapp L, et al: Pathology standards for coal workers' pneumoconiosis. Arch Pathol Lab Med 103:375, 1979
44. Naeye RL, Dellinger WS: Lung disease in Appalachian soft coal miners. Am J Pathol 58:557, 1970

45. Heppleston AG: The pathological anatomy of simple pneumoconiosis in coal workers. J Pathol Bacteriol 67:51, 1953
46. Gough J: Pneumoconiosis in coal workers in Wales. Occup Med 4:86, 1947
47. Glick M, Outhred KG, McKenzie HI: Pneumoconiosis and respiratory disorders of coal mine workers of New South Wales, Australia. Ann NY Acad Sci 200:316, 1972
48. Goldstein B, Webster I: Coal workers pneumoconiosis in South Africa. Ann NY Acad Sci 200:306, 1972
49. Policard A: The mechanism of dispersion of coal particles in the lungs of miners. Br J Ind Med 9:108, 1952
50. Heppleston AG: The pathological recognition and pathogenesis of emphysema and fibrocystic disease of the lung with special reference to coal workers. Ann NY Acad Sci 200:347, 1972
51. Parkes WR: Pneumoconiosis due to coal and carbon. In: Occupational Lung Disorders. London, Butterworths, 1974, p 217
52. Zahorski W: Pneumoconiosis dans l'industrie du graphite artificial. Proceedings XIII. International Congress on Occupational Health, New York, 1961, p 828
53. Miller AA, Ramsden F: Carbon pneumoconiosis. Br J Ind Med 18:103, 1961
54. Watson AJ, Black J, Doig AT, Nagelschmidt G: Pneumoconiosis in carbon electrode makers. Br J Ind Med 16:274, 1959
55. Cartwright J: Airborne dust in coal miners: The particle size–selection characteristics of the lung and the desirable characteristics of dust sampling instruments. In Davies CN (ed): Inhaled Particles and Vapours II, Oxford, Pergamon, 1967, p 393
56. Harrison G, Lapp NL: Electron microscopic findings in the lungs of miners. Ann NY Acad Sci 200:73, 1972
57. Wagner JC: Etiological factors in complicated coal workers pneumoconiosis. Ann NY Acad Sci 200:401, 1972
58. Gough J: Pneumoconiosis in coal trimmers. J Pathol Bacteriol 51:277, 1940
59. Reisner MTR: Results of epidemiological studies of pneumoconiosis in West German coal mines. In Walton WH (ed): Inhaled Particles III, Vol 2. Surrey, England, Unwin, 1971, p 921
60. Adamson IYR, Bowden DH: Adaptive responses of the pulmonary macrophagic system to carbon. II. Morphologic studies. Lab Invest 38:430, 1978
61. Heppleston AG: Observations on the mechanism of silicotic fibrogenesis. In Walton WH (ed): Inhaled Particles III, Vol. 1. Surrey, England, Unwin, 1971, p 357
62. Guidotti TL: Coal workers pneumoconiosis and medical aspects of coal mining. South Med J 72:456, 1979
63. Unanue ER: Secretory function of mononuclear phagocytes. Am J Pathol 83:396, 1976
64. Gross P, Braun DC, deTreville RTP: The pulmonary response to coal dust. Ann NY Acad Sci 200:155, 1972
65. McBride WW, Pendergrass EG, Lieben J: Pneumoconiosis study of western Pennsylvania bituminous coal miners. J Occup Med 5:376, 1963
66. Hart PDA, Aslett EA: Chronic pulmonary disease in S. Wales coal mines. Special Report Series 243. London, Medical Research Council, Her Majesty's Stationery Office, 1942
67. Heppleston AG, Civil GW, Critchlow A: The effects of duration and intermittency of exposure on the elimination of airborne dust from high and low rank coal mines. In Walton WH (ed): Inhaled Particles III, Vol 1. Surrey, England, Unwin, 1971, p 261
68. Nagelschmidt G, Rivers O, King EJ, Trevella W: Dust and collagen content of lungs of coal workers with progressive massive fibrosis. Br J Ind Med 20:181, 1963

69. Sweet DV, Crouse W, Crabble JV, Carlberg JR, Lainhart W: The relationship of total dust, free silica and trace metal concentrations to the occupational respiratory disease of bituminous miners. Am Ind Hyg Assoc J 35:479, 1974
70. Davies JMG, Ottery J, leRoux A: The effect of quartz and other non-coal dusts in coal workers pneumoconiosis. Part II. Lung autopsy study. In Walton WH (ed): Inhaled Particles IV, Vol 2. New York, Pergamon, 1975, p 691
71. Nagelschmidt G: The study of lung dust in pneumoconiosis. Am Ind Hyg Assoc J 26:1, 1965
72. Martin JC, Daniel-Moussard H, leBouffant L: The role of quartz in the development of coal workers' pneumoconiosis. Ann NY Acad Sci 200:127, 1972
73. Weller W: The relationship between duration of dust inhalation of a coal-quartz mixture and dust retention, lung function and pathology on rats. In Walton WH (ed): Inhaled Particles III, Vol 1. Surrey, England, Unwin, 1971, p 337
74. Schlipkoter HW, Hilscher W, Pott F, Beck EG: Investigations on the aetiology of coal workers pneumoconiosis with the use of PVN-oxide. In Walton WH (ed): Inhaled Particles III, Vol 1. Surrey, England, Unwin, 1971, p 379
75. Green F, DeNee PP, Jopling M: An SEM study of the relationship of dust composition to tissue response in coal miners' lungs. Presented at American Industrial Hygiene Association Conference. Biltmore Hotel, Los Angeles, May 7–12th, 1978
76. Reichel G, Bauer HD, Bruckman E: The action of quartz in the presence of iron hydroxides in the human lung. In Walton WH (ed): Inhaled Particles IV, Vol 1. New York, Pergamon, 1975, p 403
77. Kettle EH: The interstitial reactions caused by various dusts and their influence on tuberculous injections. J Pathol Bacteriol 35:395, 1932
78. Byers PD, King EJ: Experimental infective pneumoconiosis with *Mycobacterium tuberculosis* (var. *muris*) and hematite by inhalation and by injection. J Pathol Bacteriol 81:123, 1961
79. Rossiter CE, Rivers D, Bergman I, et al: Dust content radiology and pathology in simple pneumoconiosis of coal workers. In Davies SN (ed): Inhaled Particles and Vapours II. Oxford, Pergamon, 1967, p 419
80. Rossiter CE: Relation between content and composition of coal workers' lungs and radiological appearances. Br J Ind Med 29:31, 1972
81. Sorenson JRT, Kober TE, Petering HG: The concentration of Cd, Cu, Fe, Ni, Pl and Zi in bituminous coals from mines with differing incidences of coal workers' pneumoconiosis. Am Ind Hyg Assoc J 35:93, 1974
82. Christian RT, Nelson J: Coal: Response of cultured mammalian cells corresponds to the prevalence of coal workers' pneumoconiosis. Environ Res 15:232, 1978
83. Parkes WR: Beryllium disease. In: Occupational Lung Disorders. London, Butterworths, 1974
84. Reger R, Hancock J: Coal miners exposed to diesel exhaust emissions. Presented at Environmental Health Conference, Park City, Utah, April, 1979
85. Scheuchenko AM: The role of some physical and chemical properties of mine dust in the development of pneumoconiosis. In Walton WH (ed): Inhaled Particles III, Vol 1. Surrey, England, Unwin, 1971, p 561
86. Hahon N: Depression of viral interferon induction in cell monolayers by coal dust. Br J Ind Med 31:201, 1974
87. Hutchinson JEM: Twins with coal-workers' pneumoconiosis. Br J Ind Med 23:240, 1966
88. Heise ER, Major PC, Mentnech MS, et al: Predominance of histocompatibility antigens W18 and HL-A1 in miners resistant to complicated coal workers' pneumoconiosis. In Walton WH (ed): Inhaled Particles IV, Vol 2. New York, Pergamon, 1975, p 495
89. Higgins ITT, Oldham PD, Kilpatrick GS, et al.: Blood groups of miners with coal workers pneumoconiosis and bronchitis. Br J Ind Med 20:324, 1963

90. Heise ER, Mentnech MS, Olenchock SA, et al: HL-A1 and coal workers pneumoconiosis. Am Rev Resp Dis 119:903, 1979
91. Soutar CA, Turner-Warwick M, Parkes WR: Circulating antinuclear antibody and rheumatoid factor in coal pneumoconiosis. Br Med J 3:145, 1974
92. Lippmann M, Eckert HL, Hahon N, Morgan WKC: Circulating antinuclear and rheumatoid factors in coal miners. Ann Intern Med 79:807, 1973
93. Hagadorn JE, Burrell R: Lung reactive antibodies in IgA fractions of sera from patients with pneumoconiosis. Clin Exp Immunol 3:263, 1968
94. Burrell R, Flaherty DK, Schreiber JE: Immunological studies of experimental coal workers pneumoconiosis. In Walton WH, McGovern B (eds): Inhaled Particles IV, Vol 2. Oxford, Pergamon, 1975, p 519
95. Green GM: Lung defense mechanisms. Med Clin North Am 57:547, 1973
96. Ulmer WT, Reichel G: Functional impairment in coal workers pneumoconiosis. Ann NY Acad Sci 200:405, 1972
97. Jacobsen M, Burns J, Attfield MD: Smoking and simple pneumoconiosis. In Walton WH, McGovern B (eds): Inhaled Particles IV, Vol 2. Oxford, Pergamon, 1975, p 759
98. Naeye RL, Mahon JK, Dellinger WS: Effects of smoking on lung structure of Appalachian coal workers. Arch Environ Health 22:190, 1971
99. Wagner, JC: Immunological factors in coal workers' pneumoconiosis. In Walton WH (ed): Inhaled Particles III, Vol 2. Surrey, England, Unwin, 1971, p 573
100. Cassidy EP: The national coal workers autopsy study. Arch Pathol 94:133, 1972
101. Parkes WR: The chest radiograph. In: Occupational Lung Disorders. London, Butterworths, 1974
102. Ryder R, Lyons JP, Campbell H, Gough J: Emphysema in coal workers pneumoconiosis. Br Med J 3:481, 1970
103. Wagner JC, Wusteman FS, Edwards JH, Hill RJ: The composition of massive lesions in coal miners. Thorax 30:382, 1975
104. James WRL: The relationship of tuberculosis to the development of massive pneumoconiosis in coal workers. Br J Tuber 48:89, 1954
105. Morgan WKC, Reger R, Burgess DB, Shoub E: A comparison of the prevalence of coal workers pneumoconiosis and respiratory impairment in Pennsylvania bituminous and anthracite miners. Ann NY Acad Sci 200:252, 1972
106. Reisner MTR: Pneumoconiosis and dust exposure, results of an investigation of miners with a definite dust exposure for periods of 7 to 10 years. In Davies CN (ed): Inhaled Particles and Vapours, Vol 2. Oxford, Pergamon, 1967, p 453
107. Rae S: Pneumoconiosis and coal dust exposure. Br Med Bull 27:53, 1971
108. McLintock JS, Rae S, Jacobsen M: The attack rate of progressive massive fibrosis in British coal mines. In Walton WH (ed): Inhaled Particles III, Vol 2. Old Woking, Surrey, Unwin, 1971, p 933
109. Cochrane AL: The attack rate of progressive massive fibrosis. Br J Ind Med 19:52, 1962
110. Penman RW: Complications of coal workers pneumoconiosis. In Key MM, Kerr LE, Mundy M (eds): Pulmonary Reactions to Coal Dust. New York, Academic, 1971, p 179
111. Morgan WKC: Prevalence of coal workers pneumoconiosis. Am Rev Resp Dis 98:306, 1968
112. Vyskocil J, Tume J, Macek M: Relationships between morphological changes and content of silica and hydroxyproline in bronchi and lungs of coal miners. Int Arch Arbeits Med 26:157, 1970
113. Pratt PC: Role of silica in progressive massive fibrosis in coal workers pneumoconiosis. Arch Environ Health 16:734, 1968
114. Rivers D, James WRL, Davies DG, Thomson S: The prevalence of tuberculosis at necropsy in progressive massive fibrosis of coal workers. Br J Ind Med 14:39, 1957

115. Laqueur WA: Final report on the pathology of coal workers pneumoconiosis and related investigations (P.H.S. Grant No. 64–65–9), Beckley, West Virginia, Appalachian Regional Hospital, 1966
116. Marks J: Infective pneumoconiosis due to anonymous mycobacteria. Br Med J 2:1332, 1961
117. Gernez-Rieux C, Tacquet A, Devulder B, et al: Experimental study of interactions between pneumoconiosis and mycobacterial infections. Ann NY Acad Sci 200:106, 1972
118. Byers PD, King EJ: Experimental and infective pneumoconiosis with coal, kaolin and mycobacteria. Lab Invest 8:647, 1959
119. Steenken W, Raleich JW, Smith MM: The pathogenicity of isoniazid resistant, catalase negative, tubercle bacilli for the silicotic host (guinea-pigs). Am Rev Resp Dis 83:208, 1961
120. Gross P, Westrick ML, McNerney JM: Experimental tuberculo-silicosis, a comparison of the effects produced by some of its various pathogenic components. Am Rev Resp Dis 83:510, 1961
121. Gardner LU: Studies on experimental pneumoconiosis: Reactivation of healing primary tubercles in lung by inhalation of quartz, granite and carborundum dust. Am Rev Tuberc Pulmon Dis 20:833, 1929
122. Allison AC, Hart PD: Potentiation by silica of the growth of mycobacterium tuberculosis in macrophage cultures. Br J Exp Pathol 49:465, 1968
123. Hart JR, Cochrane AL, Higgins ITT: Tuberculin sensitivity in coal workers pneumoconiosis. Tubercle 44:141, 1963
124. Hendricks CAM, Bleiker MA: Tuberculin sensitivity in coal miners with pneumoconiosis. Tubercle 45:379, 1964
125. Ball JD, Berry G, Clarke WG, et al.: A controlled trial of anti-tuberculosis chemotherapy in the early complicated pneumoconiosis of coal workers. Thorax 24:399, 1969
126. McCallum RI: Treatment of progressive massive fibrosis in coal miners. Proceedings XIII, International Congress on Occupational Health, New York, 1961, p 741
127. Caplan A: Certain radiological appearances in the chest of coal miners suffering from rheumatoid arthritis. Thorax 8:29, 1953
128. Wagner JC, McCormick JN: Immunological investigations of coal workers' disease. J R Coll Physicians Lond 2:49, 1967
129. Gough J, Rivers D, Seal RME: Pathological studies of modified pneumoconiosis in coal miners with rheumatoid arthritis (Caplan's syndrome). Thorax 10:9, 1955
130. Benedek TG: Rheumatoid pneumoconiosis. Documentation of onset and pathogenetic considerations. Am J Med 55:515, 1973
131. Petry H: Silikose und Polyarthritis. Arch Gewerbepathol 13:221, 1954
132. Benedek TG, Zawadzki ZA, Medsger TA: Serum immunoglobulins, rheumatoid factor, and pneumoconiosis in coal miners with rheumatoid arthritis. Arthritis Rheum 19:731, 1976
133. Miall WE, Caplan A, Cochrane AL, et al.: An epidemiological study of rheumatoid arthritis associated with characteristic chest X-ray appearances in coal miners. Br Med J 2:1231, 1953
134. Caplan A, Payne RB, Withey JL: A broader concept of Caplan's syndrome related to rheumatoid factors. Thoarax 17:30, 1962
135. Noonan CD, Taylor FB, Engleman EP: Nodular rheumatoid disease of the lung with cavitation. Arthritis Rheum 6:232, 1963
136. Miall WE: Rheumatoid arthritis in Wales, An epidemiological study of a Welsh mining community. Ann Rheum Dis 14:150, 1955
137. DeHoratius RJ, Williams RC: Rheumatoid factor accentuation of pulmonary lesions associated with experimental diffuse proliferative lung disease. Arthritis Rheum 15:293, 1972

138. Spector WG, Heesom N: The production of granulomata by antigen-antibody complexes. J Pathol 98:31, 1969
139. DeHoratius RH, Abruzzo JL, Williams JC: Immunofluorescent and immunologic studies of rheumatoid lung. Arch Intern Med 129:441, 1972
140. Polacheck AA, Pijanowski WJ: Extrathoracic egg shell calcifications in silicosis. Am Rev Resp Dis 82:714, 1960
141. Caplan A: Correlation of radiological category with lung pathology in coal workers pneumoconiosis. Br J Ind Med 19:171, 1962
142. Gross P, Tuma J, deTreville RTP: Emphysema and pneumoconiosis. Arch Environ Health 22:194, 1971
143. Ferin J: Emphysema in rats and clearance of dust particles. In Walton WH (ed): Inhaled Particles III, Vol 1. Surrey, England, Unwin 1970, p 283
144. Welch WH: Cirrhosis hepatis anthracotica. Johns Hopkins Hosp Bull 2:32, 1891
145. Hartung VW, Einbrodt HJ: Lokalisation und Art der Staubablagerungen in der Lunge und ihre funktionelle Bedeutung. Beitr Silikoseforsch, S-Bd Grundfragen Silikoseforsch Bd 6:379, 1965
146. Parkes WR, Williamson RGB, Phillips TJG: Emphysema in coal workers. Br Med J 4:430, 1970
147. Resnick H, Lapp NL, Morgan WKC: Serum trypsin inhibitor concentrations in coal miners with respiratory symptoms. JAMA 215:1101, 1971
148. Hankinson JL, Reger RB, Fairman RP, et al.: Factors influencing expiratory flow rates in coal miners. In Walton WH (ed): Inhaled Particles IV, Vol 2. Surrey, England, Unwin, 1977, p 737
149. Muir DCF, Burns J, Jacobsen M, Walton WH: Pneumoconiosis and chronic bronchitis. Br Med J 2:424, 1977
150. McKenzie HI, Glick M, Outhred KG: Chronic bronchitis in coal miners: Antemortem/post-mortem comparisons. Thorax 24:527, 1969
151. Ryder RC, Lyons JP, Campbell H, Gough J: Bronchial mucous gland status in coal workers pneumoconiosis. NY Acad Sci 200:370, 1971
152. Lapp NL, Seaton A, Kaplan KC, et al.: Pulmonary hemodynamics in symptomatic coal miners. Am Rev Resp Dis 104:418, 1971
153. Sanders WL: Heart disease and pneumoconiosis. Thorax 25:223, 1970
154. Wells AL: Cor pulmonale in coal workers pneumoconiosis. Br Heart J 16:74, 1954
155. Lapp LN, Morgan WKC: Cardio-respiratory function in United States coal workers. Bull Physiopathol Resp 11:527, 1975
156. Thomas AJ, James WRL: The right ventricle and the small pulmonary arteries in coal workers. Br Heart J 20:403, 1958
157. Wood P: Diseases of the Heart and Circulation, 2nd ed. London, Eure & Spottiswoode, 1956, p 850
158. Seaton A, Lapp NL, Chang CHF: Lung perfusion scanning in coal workers' pneumoconiosis. Am Rev Resp Dis 103:338, 1971
159. Liebow AA, Hales MR, Lindskog GE: Enlargement of the bronchial arteries and their anastomoses with the pulmonary arteries in bronchiectasis. Am J Pathol 25:211, 1949
160. Kremer R: Pulmonary hemodynamics in coal workers pneumoconiosis. Ann NY Acad Sci 200:413, 1972
161. Rasmussen OL, Laqueur WA, Futterman P, Warren HD, Nelson CW: Pulmonary impairment in southern West Virginia coal miners. Am Rev Resp Dis 98:658, 1968
162. Laqueur WA, Wells HA: Right ventricular hypertrophy in bituminous coal miners in West Virginia. Lab Invest 15:1127, 1966
163. Berg J, Burbank F: Correlations between carcinogenic trace metals in water supplies and cancer mortality. Ann NY Acad Sci 199:249, 1972
164. Miller E, Miller J: In Busch M (ed): Molecular Biology of Cancer. New York, Academic, 1974, p 377

165. Yoshida T, Ito Y, Suzuki Y: Inhibition of hepatic drug metabolizing enzyme by cadmium in mice. Bull Environ Contam Toxicol 15:402, 1976
166. Berry G, Newhouse ML, Turok M: Combined effects of asbestos and smoking on mortality from lung cancer in factory workers. Lancet 2:476, 1972
167. Goldman KP: Mortality of coal miners from carcinoma of the lung. Br J Ind Med 22:72, 1965
168. Jacobsen M: Dust exposure, lung disease and coal miners mortality. Ph.D. thesis, Edinburgh University, 1976
169. Costello J, Ortmeyer CE, Morgan WKC: Mortality from lung cancer in U.S. coal miners. Am J Public Health 64:222, 1974
170. Ortmeyer CE, Costello J, Morgan WKC, Swecker S, Peterson M: The mortality of Appalachian coal miners. Arch Environ Health 29:67, 1974
171. Liddell FDK: Mortality of British coal miners in 1961. Br J Ind Med 30:15, 1973
172. Kennaway EL, Kennaway NM: A further study of the incidence of cancer of the lung and larynx. Br J Cancer 1:260, 1947
173. Rooke GB, Ward RG, Dempsey AN, Dowler JB, Whitaker CJ: Carcinoma of the lung in Lancashire coal miners. Thorax 34:229, 1979
174. Cochrane AL, Haley TJL, Moore R, Hole D: The mortality of men in the Rhonda Fach, 1950–1970. Br J Ind Med 36:15, 1979
175. Enterline PE: A review of mortality data for American coal miners. Ann NY Acad Sci 200:260, 1972
176. Enterline PE: Mortality rates among coal miners. Am J Public Health 54:758, 1964
177. Scarano D, Fadali AM, Lemole GM: Carcinoma of the lung and anthracosilicosis. Chest 62:251, 1972
178. National Institute of Occupational Safety and Health research report No. 77–155. Mortality among coal miners covered by the UMWA health and retirement funds, 1977. Rockville, Maryland, NIOSH, 1977
179. Kennaway EL, Kennaway NM: The incidence of cancer of the lung in coal miners in England and Wales. Br J Cancer 7:10, 1953
180. James WRL: Primary lung cancer in South Wales coal workers with pneumoconiosis. Br J Ind Med 12:87, 1955
181. Doll R: Cancer of the lung and nose in nickel workers. Br J Ind Med 15:217, 1958
182. Carroll R: The influence of lung scars on primary lung cancer. J Pathol Bacteriol 83:293, 1962
183. Abraham JL: Recent advances in pneumoconiosis: The pathologist's role in etiologic diagnosis. In: The Lung, IAP Monograph No. 19. Baltimore, Williams & Wilkins, 1978, p 96
184. Lamb D: Physiological/pathological correlations in coal workers pneumoconiosis. Bull Physiopathol Resp 11:471, 1975
185. Worth G, Muysers R, Einbrodt HJ: Uber die Korrelationen von rontgenologischen, pathologisch-anatomischen und staubanalytischen Befunden bei der kohlenbergarbeiter Pneumokoniose. Beitr Silikoseforsch Heft 96:1, 1968
186. Naeye RL, Dellinger WS: Coal workers pneumoconiosis: Correlation of radiologic and post-mortem findings. JAMA 220:223, 1972
187. Lyons JP, Ryder RC, Campbell H, Clarke WG, Gough J: Significance of irregular opacities in the radiology of coal workers pneumoconiosis. Br J Ind Med 31:36, 1974
188. Solu S: Disability of coal mine workers. Chest 61:306, 1972
189. Cotes JE, Deivanayagam CN, Field GB, Billiet L: Relation between type of simple pneumoconiosis (P or M) and lung function. In Walton WH (ed): Inhaled Particles III. Surrey, England, Unwin, 1971, p 633
190. Carstairs LS: The interpretation of shadows in a restricted area of a lung field on the chest radiograph. Proc R Soc Med 54:978, 1961

191. Heitzman ER, Naeye RL, Markarian B: Roentgen pathological correlations in coal workers pneumoconiosis. Ann NY Acad Sci 200:510, 1972
192. Abraham JL, DeNee PB: Lyophilised unfixed whole lungs for correlative roentgenologic-pathologic-micro-analytic study of environmental lung disease. (Abstract) Lab Invest 32:46, 1975
193. Cohen D: Ferromagnetic contamination in the lungs and other organs of the human body. Science 180:745, 1973
194. Freedman AP, Robinson SE, Johnston RF: Non-invasive magnetometric determination of lung dust loads in coal workers. Am Rev Resp Dis 117:233, 1978
195. Robinson SE, Freedman AP: Direct magnetopneumographic measurement of particle concentration and clearance in the lung. In: Proceedings of the IEEE Engineering in Medicine and Biology Society Conference: Denver, Colorado, Oct. 1979 (Frontiers of Engineering in Health Care). New York, IEEE, 1979, p 183
196. Saldanha LF, Rosen VJ, Gonick HC: Silicon nephropathy. Am J Med 59:95, 1971
197. Matolo NM, Gorishek WM, Moslander V: Coal mining and cancer of the stomach. Rocky Mountain Med J 69:44, 1972
198. Hoffmann D, Hecht SS, Ornaf RM, et al: N-nitrosonornicotine in tobacco. Science 180:265, 1974
199. Heasman MA, Lipworth L: Accuracy of certification of cause of death. London, Gen Reg Office Studies on Med and Popul Subjects, No. 20, 1966
200. Peery TM: The autopsy data bank. Am J Clin Pathol 69:258, 1978
201. Morris SC, Moskowitz WA, Silberstein SS, Hamilton LD: Coal conversion technologies: Some health and environmental effects. Science 206:654, 1979

PATHOLOGY ANNUAL

PART 2

VOLUME 15

1980

SERIES EDITORS

SHELDON C. SOMMERS, M.D.

PAUL PETER ROSEN, M.D.