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CHAPTER 4 — Part One

Pathology of the Pneumoconioses

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In recent years, the introduction of new data and the adoption of a more critical attitude have caused our concepts of the basic processes involved in the pneumoconioses to be revised. Since some of these concepts are new, it may be advantageous to outline the older, more widely held theories and contrast their main tenets with the new concepts.

Dust Deposition

Confusion may arise regarding the use of the word *deposition*. The physiologist uses the term to denote a mere impingement and transient sojourn of dust particles upon the alveolar membrane. The pathologist, on the other hand, is more likely to speak of *deposition* in terms of the permanent or quasi-permanent storage of dust particles in the lung (pneumoconiosis). In the latter sense, the particles may be intra-, or extracellular, but they are imprisoned within lung tissue whereas in the former sense, the particles are situated in *air spaces* either free or within desquamated macrophages. Nevertheless, a sharp distinction between the two categories may not always be possible. Some dust, at one time imprisoned within lung tissue, may later be expectorated; and other dust particles, although free upon the alveolar membrane, may nevertheless be effectively immured by virtue of alveolar stasis.

Alveolar Clearance

Dust particles that impinge upon the alveolar membrane are removed with a high degree of efficiency by a process known as alveolar clearance. It is only when this dust removal or alveolar clearance becomes inadequate that pathological dust deposition or pneumoconiosis begins. Thus, pathological dust deposition may occur because: The amount of dust impinging upon the alveolar membrane is ex-

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cessive, or the alveolar clearance mechanism is defective, or there is a combination of the two factors.

Mechanism of Clearance

According to the old concept, macrophages are attracted by positive chemotropism to dust particles which have impinged upon the alveolar surface. Following phagocytosis, most of the dust-laden cells migrate toward bronchioles where further transport is taken over by the ciliated surface epithelium. A smaller number of the macrophages penetrate the respiratory membrane and then migrate to lymphatic vessels which they enter in order to be transported to satellite lymph nodes. Thus, alveolar clearance is, according to this theory, based entirely upon a purposeful migration of the dust-laden cells.

This concept implies that macrophages are endowed with intelligence since no other explanation for the apparently deliberate itineraries of the cells exists. Inasmuch as many biological scientists would be reluctant to accept a theory with such an implication, a different concept has been proposed[1] based on certain observations in human lungs. These observations were concerned with indications of alveolar stasis, i.e., the accumulation of macrophages and debris, within alveoli that adjoin vessels, bronchi, scars, and other relatively rigid structures. These findings suggested that adequate respiratory excursions of alveolar walls are a *sine qua non* of alveolar clearance. Klosterkötter[2] has recently found some support for this concept when he demonstrated that rats subjected to vigorous exercise (swimming) following exposure to carbon dust had much less pigmentation of the lungs than other rats exposed to the same dust at the same time but not exercised.

Efficiency of Clearance

It has been estimated that even in a dusty atmosphere such as a coal miner is likely to encounter, the *physiologic* dust removal (by means of alveolar clearance and thence via ciliated epithelium) is highly effective since approximately 95 per cent of the inhaled dust may thereby be eliminated.

Dust Penetration

The idea of a purposeful penetration of the respiratory membrane by dust-containing macrophages has encountered objections[3] and a number of qualified investigators have expressed the belief that par-

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ticles may penetrate into the lung interstitium without the aid of cellular transport.[1, 2] Such penetration by naked particles has been demonstrated experimentally with the optical microscope[3, 4, 7] and the electron microscope.[5] The fluctuating respiratory pressures and the alveolar respiratory excursions are probably important physical factors making dust penetration of the alveolar wall possible.[3] The conditions that determine the proportion or amount of the impinged dust which will penetrate and those that determine the sites of such penetration are not known.

Lymphatic Transport

The defensive mechanisms of the lung must cope with the remaining 5 per cent or less of the inhaled and impinged dust which is not expectorated or swallowed. This remaining dust tends to be stored more or less permanently in the lung, except for that portion which is transported to lymph nodes. Opposed to the idea of macrophages seeking out a lymphatic vessel and penetrating its wall by virtue of some unknown guidance, is the concept that naked particles which have penetrated into the interstitium are transported to lymphatic vessels by tissue fluid. This fluid, normally flowing from its origin in the blood capillaries toward lymphatic channels, would readily carry suspended finely divided dust particles with it. The penetration of the naked particles into the lymphatic lumens is more difficult to explain unless open-ended channels are assumed to be present. In animals, a portion of the dust (silica) may escape the filtering action of the lymph nodes and reach the systemic circulation whence it may be deposited in the liver and spleen.

Dust Mobilization

There is clinical and experimental evidence that pulmonary dust deposits are not necessarily static and may be mobilized.[9, 10] On the clinical side are the all-too-common observations that iron ore miners and coal miners may expectorate rusty and black sputum respectively many years after exposure to these occupational dusts has ceased. In the routine postmortem examinations of hospital deaths, it is common to find lung sections in which air spaces contain large numbers of macrophages filled with black pigment even though the particular patients had been long removed from dust exposures. This is particularly pronounced in edematous regions. Occasionally air spaces are found in which the edema fluid is converted into a slurry of carbon pigment.

The experimental evidence pointing to the mobilization of dust is

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with, the alveolar wall and that such nodules enlarge at the expense of the alveolar space into which they bulge.[13, 14] Thus, according to the new evidence, it is the alveolar wall and not the interstitium of the lung which is the primary target tissue of dust particles. It is the alveolar wall that reacts to the dust, first by the sequestration of the particulates within desquamating lining cells and then by the development of dust plaques. It is noteworthy that Gardner, who previously had championed the concept of an interstitial origin of the silicotic nodule, also stated his belief during several of the Saranac Symposia that silicotic nodules originated from alveolar walls.[15, 16]

The initial reaction of the alveolar membrane to dust particles upon its surface consists of phagocytosis by the surface cells which thereupon retract their cytoplasmic extensions, round up, and desquamate.[17] While unattached and free to move about by ameboid activity, these cells presumably continue their phagocytic activity for a time and thereby tend to keep the alveolar membrane free of particulates. The cells that desquamate from the alveolar membrane are replaced by new ones. Under some conditions, multiplication of alveolar cells proceeds at an exaggerated rate with the result that the cells are no longer flattened but more cuboidal in shape. However, the boundaries of the proliferated cells are frequently not distinguishable so that portions of such a surface may be syncytial in character. With continued stimulation by dust particles, the proliferated alveolar cells may fail to desquamate following phagocytosis of the dust. These nondesquamating cells thus form the beginning of a dust plaque. The size of the plaque is determined by the continued proliferative activity without desquamation of the alveolar cells, and the maintenance of its integrity is aided by the development of a reticulin framework between the cells.

The tendency of dust deposits to localize near vessels and bronchi is probably related to the fact that dust and debris have a greater tendency to stagnate (diminished alveolar clearance!) in those regions. Diminished alveolar clearance, in turn, is believed to be caused by the limitation in excursionary activity of those alveolar walls that are attached to relatively rigid structures such as bronchi and vessels.

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based largely on the demonstration of quartz dust in normal or near-normal portions of the lung as long as one year after the exposure (intratracheal injection) while close-by silicotic nodules are demineralized.[11]

Mechanism of Dust Mobilization

Conditions under which capillary endothelium becomes permeable and allows the escape of fluid from the blood into surrounding tissue spaces also favor the mobilization of dust deposits. Since the direction of the flow of edema fluid is from vessels toward the air spaces, extracellular dust particles caught in the flood of this fluid tend to be swept toward the air spaces. Certain mechanical factors aid in this process. Tissue fibres forming a lattice work that normally tends to impede the transport of cells and particulates, are forced apart by edema, thereby widening the interstices and facilitating such transport. The pressure and velocity of edema [redacted] be quite high, certainly higher than the normal pressure and velocity of tissue fluid.

Dust deposits that are not collagenized such as those composed of carbon, clay, and others formed by so-called inert dusts, consist mainly of dust-filled cells and reticulin fi[redacted] a matrix of structureless, proteinaceous material. The la[redacted] ntain a variable amount of extracellular dust in va[redacted] of agglomeration. In the presence of edema, the matrix becomes diluted or thinned and the extracellular dust agglomerates become more finely dispersed. Because the reticulin fibers that support the cells of the dust deposits are extremely soft and pliable and disintegrate readily, the dust-filled cells become loosened.[12] Those of the cells situated at the periphery of the deposits, deprived of support, may desquamate into the air spaces.

Alveolar Reaction to Dust

In the past, the interpretations of histopathologic observations by numerous investigators have, as a whole, agreed that the pneumoconiotic process begins with the migration of the dust-laden macrophages into the lung interstitium where the inflammatory reaction subsequently has its origin. This, of course, suggests that the interstitium of the lung is the primary target tissue responsive to the dust. Most frequently mentioned in this connection are lymphoid foci distributed throughout the lung and perivascular lymph spaces as well as obstructed intrapulmonary lymph vessels.

However, it has recently been demonstrated that very early experimental silicotic nodules develop as plaques upon, and integral

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CHAPTER 4 — Part Two

Pathology of Silicosis

Definition of Silicosis

Silicosis is a nodular pulmonary fibrosis caused by the presence within the lung tissue of crystalline silica dust particles, mainly two microns or less in diameter.

Theories of Pathogenesis

Older Theories: After it had been established that silicosis is caused by silicon dioxide (silica) in crystalline form, it became necessary to explain why this material, so inert chemically, is biologically active. The first, a mechanical theory, postulated that the sharp edges and spicules of the crystals deposited in the lungs traumatized the tissue and the nodular fibrosis resulted from the inflammatory response to this trauma. This concept was discarded in favor of the [redacted] theory which held that the very slight solubility of silicon dioxide in tissue fluid was sufficient to form an appreciable amount of silicic acid which, in turn, was responsible for the formation of scar [redacted]e. The lack of parallelism between the solubility of [redacted] forms of silica and their ability to evoke fibrous tissue [redacted] lost this theory most of its adherents. A Piezo-electric [redacted]y briefly under consideration, was based on the fact that asymmetric crystals had the property, when put under strain, to generate a [redacted] amount of electricity. Such electric current was presumed to be formed by silica crystals in the moving lung tissue and fibrosis was considered to be secondary to the electricity.

Newer Theories: The theory presently under investigation involves "surface activity." The surface of crystalline silica is believed to possess electrical charges due to unsatisfied valences, which cause denaturation of adsorbed tissue proteins and thereby stimulates fibrosis. The denatured proteins function as antigens to cause antibody production.

Antigen-antibody interaction as the most significant mechanism responsible for silicotic fibrosis is also the mainstay of the theory evolved by Vigliani and Pernis.[1] These investigators consider silicosis to be a disease of auto-immunity (similar to chronic thyroiditis

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and certain hemolytic anemias). According to this theory, crystalline silica within macrophages causes regressive cellular changes by virtue of its surface activity which lead to the formation of intracellular lipoproteins. When the macrophages die and disintegrate the liberated lipoproteins, being antigenic, stimulate antibody production. The hyaline centers of silicotic nodules have been reported by Vigliani and Pernis to consist in large part of beta and gamma globulins derived from blood plasma, thus giving strong support to their theory involving the interaction of antigen and antibody.

Gross Anatomy

A silicotic lung, depending upon the severity of involvement, may not have the usual degree of postmortem collapse due to a reduced pliancy and therefore may appear to be large. It is usually pigmented gray to black, depending upon the nature and amount of other dusts which are usually associated with the inhaled silica. The pleura is often smooth and glistening with less extensive involvement but it may be focally opaque due to subpleural fibrosis. In the later stages, pleural adhesions are frequent. Hard nodules, 2 to 4 mm. in diameter, are palpable throughout the lung. They may be uniform in distribution or more numerous in the upper than in the lower portions of the lungs. The nodules are sharply defined on the cut surface, composed of a dense, hard, gray to black tissue which projects above the surrounding, retracted, somewhat emphysematous tissue. There may be coalescence of nodules, particularly in the upper lobes. Larger nodules may be necrotic or calcified in the center.

The hilar lymph nodes are moderately enlarged, black and stony hard. The cut surface is gritty and dense. These nodes may be densely adherent to bronchi and vessels and may compress these structures so as to cause bronchial stenosis or vascular disturbance.[2, 3]

Morphology of the Silicotic Nodule

Human silicotic nodules are characterized by concentrically arranged, acellular collagenous tissue and a hyaline center. On the periphery of the nodules there is frequently a cellular zone which has been aptly named the "reactive zone."[4] The hyaline center has been found to consist in large part of plasma proteins.

The peripheral reactive zone may be narrow or wide, smoothly rounded or stellate. When one or more other types of dusts are associated with the crystalline silica, these are frequently concentrated

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in the peripheral reactive zone and may lend a pigmented appearance to the latter. The reason for this concentration of other dusts on the periphery of silicotic nodules is the interference with alveolar clearance in adjoining alveoli caused by the rigidity of the silicotic mass (See Mechanism of Alveolar Clearance).

In early or minimal silicosis, the alveolar tissue between the nodules is substantially normal.

Morphogenesis of the Early Silicotic Nodule

Based on observations in experimental animals, a silicotic nodule begins as a focal proliferation of aveolar [illegible]ing cells that have ingested silica particles and have remain[illegible] to the alveolar wall.[5] Such proliferated cells rapidly [illegible] a supporting reticulin stroma. The frequent perivascul[illegible]ion of the nodules is due to the tendency of dust and de[illegible]agnate in the alveoli surrounding vessels. The abutting a[illegible] walls here acquire masses of coherent proliferated alveolar cells which not only fill and obliterate the perivascular alveoli but often overdistend them and thereby compress the adjacent [illegible] spaces. Basically, therefore, silicosis is a focal proliferative and obliterative alveolitis which tends [illegible]eneralized only la[illegible] the disease as interference with the [illegible] mechanis[illegible]ung (alve[illegible]ce) multiplies. In time, as the cellular[illegible] of the nodules diminishes and the collagen content increases, the central vessel may become obliterated.

Significance of Peripheral Reactive Zone

When the peripheral reactive zone is non-existent or nearly so, the nodule should be considered quiescent. If a significant peripheral zone is present about a silicotic nodule, this could be indicative of the following:

a. Activity (progression) of the silicotic process[16]
b. The presence of other dusts in addition to crystalline silica[7]
c. The presence of an inflammation due to other causes, usually tuberculosis.
d. The combination of two or all three of these factors.

In human lungs, a wide peripheral reactive zone frequently has a stellate outline. Such a stellate zone has been considered pathognomonic of an associated tuberculous component[4] and also of a mixed-dust silicosis.[8]

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Distribution of Silica in Lung

Topographic distribution studies of the acid-insoluble ash associated with the nodules is concentrated largely in the peripheral reactive zone.[7] Although this is the rule, exceptions are frequent enough. The mechanism whereby this shift of dust from the center to the periphery of the silicotic nodule comes about is that which is responsible for the mobilization of dust in general (See Mechanism of Dust Mobilization).

Progression

As a result of dust mobilization, crystalline silica particles once safely sequestered within the nodule may find themselves again free in the air spaces.[8] From here, a major portion of the mobilized dust may be removed from the lung via the ciliated epithelium, and a smaller fraction left behind may later penetrate the interstitium to be carried by tissue fluid to lymphatic channels and from there to lymph nodes. The dust remaining in the air spaces may then cause the formation of new lesions. Regarding the latter, Gardner[9] stated nearly 30 years ago, "The presence of an infectious process in the lung facilitates the mobilization of dust, and metastatic foci develop early and in great abundance." The removal of silica from the lung via the ciliated epithelium thus accounts for the fact that some manifestly silicotic lungs contain no more, or even less, silica than some non-silicotic lungs. The mobilized silica, which is merely shifted from the center to the periphery of the nodule, may intensify the inflammation in the latter region and thereby extend its peripheral limit, thus accounting in part for the growth of the nodule.

Diffuse Alveolar Fibrosis

In regions of severe silicotic involvement where nodules have become crowded and to some extent confluent, there is a tendency for alveolar walls between nodules to become thickened by collagenous tissue. This results in the obliteration of the capillaries within those walls.

Pulmonary Lymphatic Obstruction

It has been taught that silicotic inflammation causes pulmonary lymphatic obstruction. The latter prevents the transport of silica particles from the involved regions. Alveolar stasis therefore develops which, in turn, is followed by diffuse alveolar fibrosis.[10]

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However, if it were true that silicotic inflammation causes pulmonary lymphatic obstruction, then pulmonary edema would be a common finding in silicotics. Yet, it is common experience that uncomplicated silicotic lungs are "dry" lungs. Therefore, the concept of lymphatic obstruction in silicosis is untenable.

A different explanation for the development of diffuse alveolar fibrosis must therefore be evolved. The simplest and, at the same time, logical explanation is that as silicotic nodules become larger and more numerous, the respiratory excursions of more and more intervening alveoli become restricted and their dust clearance correspondingly impaired. Thus, extensive alveolar stasis of silica particles develops which results in a diffuse alveolar reaction. A corollary to this concept is that a manifestly silicotic lung is more vulnerable to further dust exposure than is a normal or near-normal lung.

Associated Lesions

The most serious and at the same time, the most common lesion associated with silicosis is tuberculosis. Until about 25 years ago, it was commonly estimated that 75 per cent of the silicotics developed a superimposed tuberculosis. No newer estimates are available that would reflect the changes which have taken place due to the introduction of public health measures and specific chemotherapy as well as more energetic surgical procedures in the treatment of tuberculosis. Many observers have expressed the opinion that most, if not all, confluent silicotic lesions are due to a superadded tuberculosis.[11] A similar opinion has been expressed by some regarding the progressiveness of silicosis.[12]

A second, much less frequent and less serious complication is that of emphysema. In the earlier stages of silicosis, emphysema is generally absent or not significant.

In severe conglomerate silicosis, there is commonly considerable emphysema often with appreciable alveolar fibrosis. The consequent diminution of the capillary bed as well as vascular sclerosis results in hypertrophy and dilatation of the right heart (cor pulmonale). Sclerosis of larger vessels is not uncommon in the proximity of silicotic nodules,[13] particularly when the vessel walls are infiltrated by the silica dust particles.

It is generally agreed that the presence of silicosis does not predispose to pulmonary cancer.

Immunologic Aspects

The proclivity of silicotics to develop a superimposed tuberculosis

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has unquestionably an immunologic basis. Vigliani and Pernis believe that in tuberculo-silicosis there is a reciprocal non-specific enhancement of immunologic responses.[1] This enhancement has been demonstrated repeatedly experimentally.[14, 15] In this connection, it is of interest that the lesion of tuberculo-silicosis has been produced experimentally without living tubercle bacilli.[16] Progressive massive fibrosis of the lungs with cavitation has been produced in guinea pigs by injecting a non-fibrogenic quartz dust with formalin-killed tubercle bacilli intratracheally. Similar tuberculo-silicotic lesions but without cavitation have also been produced by the same technique and with the same non-fibrogenic dust but in combination with P.P.D. tuberculin instead of tubercle bacilli.

Another interesting immunologic aspect is the relation of silicosis to the susceptibility to bacterial pneumonia. The possibility of such relationship has practical forensic implications. However, this relationship has been denied on clinical grounds[18] and two groups of investigators independently found no support for such relationship experimentally.[19, 20] As a matter of fact, it was found in both laboratories, using different animal species, that normal animals had a higher mortality rate to pneumococcic pneumonia than did silicotic animals. The explanation of this paradoxical situation is probably related to the tendency for silicotic animals to develop a more vigorous antibody response than normal animals as was demonstrated by Pernis and Bolis.[21]

Inhibition of the Biologic Effect of Silica

Certain dusts, which include those of iron (oxide or hydroxide?), aluminum (the metal and the hydroxide), and gypsum, have the ability to modify or inhibit the biologic action of crystalline silica. Although at one time this protective action was thought to be adequately understood,[22, 23] discrepancies have arisen which now require reinvestigation of the mechanism by which the fibrogenic effect of crystalline silica is inhibited.[24] This question, in addition to its academic interest, also has practical implications inasmuch as one of these dusts (aluminum) has been employed on a limited scale in industry for the prophylaxis of silicosis.

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CHAPTER 4 — Part Three

Pathology of Asbestosis

Our present concept of the pathogenesis and histogenesis of asbestosis is based mainly upon the experimental work of the Saranac group of workers under the guidance of Gardner[1] and more particularly upon the relatively recent summarization of previous findings and extended results by Vorwald et al.[2] There is a dearth of basic information on this subject from other laboratories.

According to Vorwald et al[2] the early asbestotic lesion in the human lung consists of peribronchiolar fibrosis and on the basis of this premise these investigators have become convinced that they have reproduced the experimental counterpart of the human asbestotic lesion in animals. By the same reasoning, they have also arrived at definitive conclusions regarding the pathogenesis of this disease.

The hallmark of asbestosis in the human lung is diffuse fibrosis of the walls of air spaces associated with asbestos bodies. This fibrosis has been loosely designated as "alveolar" fibrosis. There is, in addition, a concomitant pronounced perivascular and peribronchial fibrosis as well as fibrosis of the interlobular septa and of the pleura. Emphysema is usually present in the involved parenchyma. It is characteristic of the advanced stage of asbestosis to demonstrate roentgenologically the greatest involvement at the bases of the lungs. The asbestos bodies consist of symmetrical, club-shaped, golden-brown structures, usually segmented averaging 3 to 5 μ thick and 20 to 50 μ long. It is worthy of emphasis that the mere presence of asbestos bodies is *not* pathognomonic of asbestosis even though the earlier literature has devoted much space to their appearance, genesis, and significance. The presence of these "curious bodies" as they were once called, simply indicates exposure to and inhalation of asbestos fibers.

The asbestos bodies are believed to be formed by the adsorption of proteins upon asbestos fibers in conjunction with endogenous iron, the latter giving the structures their characteristic, golden-brown color. They may be found free in the air spaces or embedded within interstitial tissue but rarely in lymph nodes. Naked asbestos fibers are also frequently seen in the interstitial tissue near asbestos bodies. Vorwald et al.[2] believe that an asbestos fiber which has been

converted into an asbestos body is no longer capable of producing tissue injury.[2] The term *asbestos* body is preferred to "asbestosis" body because the former does not imply the existence of asbestosis. The term, asbestos body in contradistinction to asbestosis body was first used by Schuster.[3]

There is no question but that the experimental work at the Saranac Laboratory, first under the guidance of Gardner and later under Vorwald's direction, represents the most laborious and comprehensive investigation of asbestosis to date. Unfortunately, in spite of the claim that the peribronchiolar fibrosis produced in the animals is equivalent to the early human asbestotic lesion, there is little resemblance of this experimental lesion to that which is found in the symptomatic asbestos worker.* Nevertheless, the diffuse pulmonary fibrosis as it may be found in human asbestosis has been described in a dog by Schuster.[3] This dog had lived in an asbestos factory for 10 years. It is also unfortunate that opportunities to examine early human asbestotic lesions have been rare indeed. There is therefore a need to confirm Gardner's and Vorwald's observation and to document more fully the early asbestotic lesion in the human lung as well as the subsequent developments leading to the fully developed diffuse pathologic entity.

Asbestosis, like silicosis, may occur as a component, either major or minor, in pneumoconioses due to mixed dusts. These dusts, in addition to asbestos, frequently consist of one or more of the following: various silicates, cement, carbon, and silica. In the mixed pneumoconioses, depending upon the nature of the other dusts, it may be very difficult to decide how much of the observed fibrosis is caused by asbestos dust and how much by one or more of the other dusts present.

The relatively pure asbestotic lesion may occur in two forms, as an actively proliferating, interstitial pneumonitis or florid type, and as an inactive, "burned-out," relatively acellular interstitial pneumonitis in which the septal walls are heavily collagenized. The latter is much more frequently encountered (in my experience).

In the florid type of asbestosis there is a very active proliferation of alveolar cells many of which remain attached to the septal wall

*Dr. Ian Webster of the South African Institute for Medical Research informed me that his laboratory has recently successfully reproduced the human type of asbestotic lesions in animals. However, this work has not as yet appeared in print.

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and are associated with a supporting reticulin stroma. This stroma is integral with the axial reticulin of the septal wall. Many of the proliferated cells have become detached and give the air spaces the appearance of what has been termed a desquamative pneumonia or alveolar catarrh. The thickening of alveolar walls by the cohesive, proliferated alveolar cells with their supporting reticulin stroma constitutes an accretive type of interstitial pneumonitis.[4] Depending upon the degree to which the cells become multilayered, the air spaces may become reduced and some, even obliterated.

There is also an expansive type of interstitial pneumonitis[5] in florid asbestosis. This is characterized by an edematous widening of the space between the basement membrane of the alveolar capillary and that of the alveolar surface epithelium. Low[5] as well as Policard and Collet[6] and Schulz[7] have demonstrated this space beautifully with electron photomicrographs. Concomitant with the edematous widening of the intermembranous space there is an increase in reticulin fibers within the space. Because the expansive widening of the alveolar wall is limited, there is no significant narrowing of air spaces by this type of pneumonitis.

In the inactive, "burned-out," type of asbestosis, the type most often seen at autopsy, the walls of the air spaces are thickened by collagen and are essentially acellular. The air spaces are generally greatly enlarged. What the anatomical designation of the large air spaces might be is difficult to determine. Their large size precludes their consideration as alveoli. What happened to the alveoli and by what process these structures had disappeared is not known.

A very important and, at the same time, interesting feature of asbestosis is the status of the pulmonary capillary bed. The teaching has been that the main defect in pulmonary function in asbestosis is an alveolo-capillary block and this has been explained on the basis that there is an interposition of collagen or cells between the capillary wall and the free surface of the respiratory membrane. Theoretically, it should be relatively simple to demonstrate such a basic lesion. However, in practice this demonstration is difficult. When a septal wall has undergone collagenous change, the capillary is often difficult to demonstrate. In other situations a plethora of capillaries may suggest an angioma-like appearance upon one or both surfaces of collagenized septal walls similar to the condition described by Pratt.[8] Such capillaries may be very distended, and often expose more than one-half of their cylindrical surface to the alveolar lumen on *one side of the septal wall only*. Usually, the apparently free surfaces of the capillaries show no suggestion of mural thickening. With

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such vastly different and divergent pictures represented in histopathological preparations it may be difficult to maintain that there is morphologic support for the functional concept of alveolo-capillary block.

Progression

The literature contains diametrically opposed statements in regard to the progressiveness or non-progressiveness of asbestosis. The only systematic and factual study of this problem was made by Lynch and Cannon.[9] In this paper, 40 autopsied cases of asbestosis were classified and correlated with regard to the presence or absence of fresh fibrosis (florid asbestosis) or old fibrosis (burned-out asbestosis) and the duration as well as the recency of the exposure. These investigators write, "In this series occurs evidence that the disease does not progress beyond a limited time after exposure to asbestos dust ceases. . . ." This conclusion received additional support in the incineration studies of Gross and Smith[10] who found that the amount of acid-insoluble ash in asbestotic lung tissue was, at best, exceedingly scanty and that by virtue of the fibrous character of the dust, it was not readily mobilized during intercurrent episodes of edema and therefore progression (in the sense of the development of new inflammatory dust foci) did not occur.

Opinions to the contrary are either *ex cathedra* statements without supportive evidence, or the evidence rests solely upon clinical or X-ray interpretations without histopathologic substantiation.

There is little doubt but that some asbestotic patients may develop increasingly severe dyspnea even after removal from further dust exposure. It would, however, be improper to assume from such deterioration of the clinical status that the pulmonary fibrosis due to asbestos dust has progressed. Quite commonly it is an associated emphysema and cor pulmonale which account for the increasingly severe dyspnea.

Complications

It is not an uncommon fault of medical writers to use sporadic concomitant findings as the sole basis for claiming an etiologic relationship. Such claims have been made or implied without evidence for many conditions found associated with asbestosis. It is interesting to note for instance, the stress placed by several earlier writers on the presence of bronchitis, bronchiectasis, abscesses, bronchopneumonia, and even tuberculosis in association with asbestosis. Although a relationship between tuberculosis and silicosis has been proven

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clinically as well as experimentally, no such relationship has been established for asbestosis and tuberculosis. As a matter of fact, such clinical relationship has been denied[11] and the experimental evidence is also not supportive of this view.[2]

In recent years, the association of pulmonary carcinoma with asbestosis has been the topic of many publications.[12] It seems only proper to expect the same rigorous criteria for the establishment of etiologic relationship between pulmonary cancer and asbestos as have been demanded for the proof that pulmonary cancer is caused by excessive cigarette smoking.

In a careful study which involved such a rigorous application of recommended criteria, it was found that an etiologic relationship between pulmonary cancer and asbestosis did not exist among asbestos miners in the Canadian province of Quebec.[12]

However, Doll's study (in collaboration with J. F. Knox)[13] showed that in a large plant of the textile asbestos industry in England there had been a hazard of pulmonary cancer in 113 male asbestos workers employed for 20 years or more. The risk of lung cancer was about 10 times that expected in the general population. The study also included details of 105 consecutive coroner's necropsies on asbestos workers performed between 1935 and 1953. It included all cases in which asbestosis might have been considered a contributory cause of death. Among these were 15 primary lung cancers associated with asbestosis and 3 primary lung cancers without associated asbestosis. The latter 3 cases occurred in men whose asbestos dust exposure was 12 years or less and after dust control laws became effective. Since the adoption of these laws, there appears to be no evidence that a hazard continues to exist under the working conditions now prevailing in England.[14]

In the United States, sporadic reports of primary lung cancer associated with asbestosis have appeared,[15, 16] most of these cases occurring in people engaged in asbestos textile fabrication or in the installation of pipe insulation.

The development of chronic fibrous and often obliterative pleuritis as well as of lobular septal thickening is very common in asbestosis. Nevertheless, the absence of such pleuritic changes has been noted in cases of manifest asbestosis.[9] The cause of this chronic fibrotic inflammation is difficult to fathom since asbestos fibers, as a rule, are not demonstrable in this fibrous tissue.[9]

Because of the inconstancy of occurrence, Lynch and Cannon[9] suggested that the pleuritic process in asbestosis may be a secondary phenomenon. Another possibility which may be considered is based

on the apparently metastatic character of the fibrosis which suggests that the fibrous reaction is due to a generalized hyperactivity of pulmonary connective tissue cells induced by asbestos fibers. This excessive fibroplasia could be a part of a response to a hypersensitivity to these fibers.

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CHAPTER 4 — Part Four

Pathology of Anthracosis

In fully developed or severe anthracosis, the pulmonary dust deposits are large and confluent so as to render the pleural as well as the cut surface diffusely and uniformly black. In less severe cases, the deposits of soft-coal dust or of carbon may be discrete and small thereby giving the lung a mottled appearance.

Deposits of pure carbon or of soft-coal dust without the admixture of silica may be impalpable unless the vessel, bronchus, or bronchiole about which such foci commonly occur, is palpable. Because of the presence of one or more complicating factors, severely anthracotic lungs may exhibit extensive induration, pleural adhesions, deforming scars, as well as emphysema with or without bulla formation.

The hilar lymph nodes are slightly to moderately enlarged, of variable consistency, and they present homogeneous to variegated, jet-black, moist to dry cut surfaces depending on the presence or absence of other associated disease factors.

Carbon and soft-coal dusts are classified as inert because these dusts do not evoke a significant fibrous reaction. Microscopic examination of anthracotic foci reveals fine reticulin fibers coursing between large, pigmented cells and the presence of only rare, delicate collagen fibers.

The genesis of an anthracotic plaque has recently been described by Hulse[1] as a proliferation of alveolar surface cells upon the alveolar wall. These cells, although filled with ingested dust particles, do not desquamate but remain cohesive and an integral part of the alveolar wall. Reticulin fibers, intimately associated with the proliferated alveolar cells, form a supporting stroma for the growing plaque. Initially, most, if not all, of the dust is intracellular. With the lapse of time, some of the original cells die and disintegrate rendering the dust extracellular. Although much of the dust may be rephagocytosed, some may remain extracellular. The flow of tissue fluid may transport the latter toward lymphatic vessels and some of the particles may become trapped in the periadventitial tissues of vessels and bronchi as well as in the adventitia itself.

Since anthracotic deposits contain very little or no collagen, they are very vulnerable to the erosive action of edema and acute inflam-

Pathology of the Pneumoconioses (1960)
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mation which tend to disrupt the foci and liberate the dust. This is the explanation why former coal miners, many years removed from dust exposure, may continue to cough up black sputum.

The most common and also the most important complication associated with severe anthracosis is emphysema which may become so extensive as to cause invalidism, cor pulmonale, and death from right heart failure. To Gough[2] belongs the credit for establishing the relationship between emphysema and the dust deposits. By means of a special technique, Gough[2] was able to demonstrate grossly discernible emphysematous foci each of which consisted of obviously enlarged air spaces clustered about black pigment deposits. This emphysema was therefore designated as "focal" in contrast to the lobular variety. According to Heppleston,[3] one of Gough's co-workers, this focal emphysema is the dilatation of respiratory bronchioles caused by a combination of two circumstances: The failure of alveoli obstructed by dust to expand causes increased traction on the wall of the corresponding respiratory bronchiole during inspiration and atrophy of the smooth muscle of bronchioles has been observed in the regions of dust deposition. As a result of the smooth muscle deficit, the normal shortening and constriction of such bronchioles do not take place during expiration. Contrary to most accepted views regarding the anatomic changes in emphysema, Heppleston does not consider damage to elastic tissue as a major factor.

It is important to bear in mind that the "focal" emphysema associated with deposits of soft-coal dust is of the non-obstructive type and therefore asymptomatic except in cases of severe anthracosis.

A second serious but less frequent "complication" than emphysema is the occurrence of extensive, massive pulmonary fibrosis. This condition has been designated as "progressive massive fibrosis" of the lungs or P.M.F. in England where it was considered to be an "infectious" pneumoconiosis, probably of tuberculous character.[4] As a matter of fact, in 30 to 40 per cent of such cases, tubercle bacilli were demonstrable either tinctorially or by culture.[4] On the European continent and in the United States, however, this pulmonary fibrosis in coal miners has not been considered a "complication" of anthracosis but rather the result of an admixture of crystalline silica in the coal dust, therefore, an anthrasilicosis (or anthracosilicosis).

The well-designed experiments conducted in E. J. King's laboratory have clearly demonstrated that silica-free soft-coal dust in conjunction with a tuberculous infection of low virulence may produce a pulmonary fibrosis in guinea pigs which is comparable to the P.M.F. of coal workers.[5] Following this remarkable demonstration, a

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similar characteristic, synergistic inflammatory response has also been demonstrated with *massive* pulmonary deposits of other dusts in association with a tuberculous infection.[6] These demonstrations justify the use of the generic term, tuberculopneumoconiosis of which tuberculosilicosis, tuberculokaolinosis, and tuberculoanthracosis are specific examples.

There is little question but that some of the cases designated as anthracosilicosis on the European continent as well as in the United States probably belong in the category of tuberculoanthracosis or P.M.F. (infectious pneumoconiosis) of the English designation. This probability exists because the diagnosis of anthracosilicosis has usually been made on a presumptive basis; without chemical, mineralogical, or X-ray diffraction analysis of the lung ash. In the United States, for instance, it has been customary to *assume* the presence of fibrogenic silica in anthracotic lungs that contained dark gray to jet-black, dense, hard fibrous masses; just as it now seems proper in England to *assume* the presence of a tuberculous infection when confronted with similar findings even though tubercle bacilli may not be demonstrable by any known method.

The principal histopathological alteration in the tuberculopneumoconioses is a wide-spread accretive-type of chronic interstitial pneumonitis[7] which results in alveolar obliteration. This obliteration is caused by a tissue composed of proliferating alveolar cells and their associated network of reticulin fibers. With the maturation of the proliferated alveolar tissue, collagen fibers appear and the cellularity diminishes as the collagen content increases. Focal necrosis may occur, followed by liquefaction and cavity formation.

When the tuberculous infection is of relatively low virulence, the characteristic microscopic features by which a tuberculous inflammation can usually be recognized may be absent. No tubercles may be found. Opacity of the dust and the great density of its distribution (*massive* dust deposits are a *sine qua non* of all tuberculopneumoconioses with the exception of tuberculosilicosis) are additional reasons for the occultation of the infectious process.

Obversely, the existence of a silicotic inflammation may also be modified and rendered occult by the presence of other dusts to the point at which no discrete silicotic nodules are formed.[8] Also, because the microscopic anatomy of a tuberculous inflammation and that of a silicotic inflammation have many features in common, further difficulties may be encountered in the identification of a probable silicotic component in anthracotic pulmonary inflammatory tissue, particularly if the tissue is opacified by the dust.

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From the foregoing, it is apparent that on the basis of histopathologic criteria it may be difficult to establish or to exclude either a tuberculous or a silicotic component in anthracotic pulmonary fibrous inflammatory tissue under certain conditions. Other criteria may also fail to be helpful. For example, the demonstration of acid-fast bacilli does not necessarily signify that they are tubercle bacilli. Nor does the failure to demonstrate the organism necessarily rule out its presence. On the other hand, the demonstration of free silica in the lung ash does not necessarily establish the presence of silicosis; but neither does the lack of more than 1 per cent of crystalline silica in the lung ash rule out the existence of a silicotic component.

In spite of the beautiful experiment demonstration by the investigators under E. J. King's direction, that a massive pulmonary fibrosis may be caused by coal dust in combination with a tuberculous infection,[5] it would be illogical to classify all cases of P.M.F. as tuberculous and to ignore the role of silica as exemplified by those cases of massive pulmonary fibrosis which had long-term exposure to high concentrations of crystalline silica in addition to coal dust and yet had no bacteriological evidence of a tuberculous infection or actually had negative tuberculin tests.[9] Even the presence of cavitation may not be interpreted as *prima-facie* evidence of a tuberculous component since ischemic necrosis may also produce such cavitation.[10]

Since Caplan[11] described round, well-defined nodules of homogeneous density in the chest roentgenograms of some coal miners who had rheumatoid arthritis, other observers described similar lesions in coal miners.[12] Microscopic examination of such a lesion has revealed the granulomatous inflammation typical of the rheumatic nodule. This finding suggests that the enhancement of immunologic response of pulmonary tissue to tuberculosis, attributed by Vigliani[13] to crystalline silica, may also be true for coal dust in respect to rendering the pulmonary tissue responsive to the rheumatoid antigen.

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CHAPTER 4 — Part Five

Pathology of Diatomite Dust Pneumoconiosis

The basic changes found in human lungs exposed to natural diatomite dust are very similar to the reaction of animal lungs to amorphous silica dust.[1, 2] This reaction, which is a diffuse one without nodulations, consists of an accretive, non-collagenous type of chronic interstitial pneumonitis[3] combined with the accumulation of desquamated alveolar cells. The characteristic features of this inflammation include a multiplication of alveolar cells which, accompanied by a reticulin framework and remaining cohesive, form an integral part of the alveolar wall and thereby diminish the alveolar space to the same extent to which they thicken the wall.[3] The alveolar mural thickening leads to impaired alveolar respiratory excursions which result in diminished alveolar clearance. Diminished clearance, in turn, together with an excessive desquamation of alveolar cells causes alveolar stasis.[4] Because of widespread alveolar stasis, many of the air spaces are filled, often to the point of obliteration, with alveolar cells and their debris. By an incineration technique a large amount of mineral dust is found not only within the thick alveolar walls but also within the alveolar debris and even within the walls of blood vessels.[5]

In contrast to the non-fibrogenic natural diatomite dust, the flux-calcined diatomite does cause the formation of dense collagenous masses in the lungs. This fibrogenic potential is related to the conversion of amorphous silicon dioxide by high temperatures during the calcining process to crystalline forms such as cristobalite and tridymite. The latter possess an even greater potential for the production of collagen than the more common quartz.[6] The pulmonary fibrosis in workers who have inhaled significant amounts of flux-calcined diatomite dust is not nodular but occurs as irregular coalescent masses which tend to be most pronounced in the upper portions of the lungs. It should also be kept in mind that the fibrous masses are superimposed upon the diffuse cellular alveolar thickening induced by the non-crystalline components of diatomite dust. In addition to this disturbance, that portion of the lung tissue which is rela-

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tively free of dust may become damaged—not by fibrosis, but by emphysema, and some of the latter may be bullous. Pneumothorax may result from rupture of an emphysematous bulla.

It has recently been demonstrated experimentally that the pulmonary inflammatory reaction to a silica dust which is ordinarily nonfibrogenic will, in the presence of a tuberculous infection, develop foci of collagenization.[7] Similarly, it was discovered that collagenization also develops when a small weight of dead tubercle bacilli or merely tuberculin is substituted for living organisms.[8] Although the first portion of these demonstrations is the experimental counterpart for the clinical observation that the development of coalescent fibrous masses is frequently on a tuberculous basis, the other aspects of these experiments suggest that basically the development of collagen under these circumstances is the result of an exaggerated antigen-antibody reaction.[9] If that be the case, then antigen-antibody reactions provoked by infections other than those causing granulomatous inflammations may conceivably cause similar pathologic and roentgenologic changes.

Some support for this concept has been found in animals exposed to non-fibrogenic dusts which develop extensive diffuse interstitial fibrosis in the presence of spontaneous chronic infections (bronchitis with perifocal pneumonia), lesions which in non-dusted animals provoke only limited or no fibroplasia. There is no doubt that a proportion (magnitude unknown) of workers with coalescent, dense, fibrous masses in the subapical regions of pneumoconiotic lungs do not have a tuberculous infection since negative tuberculin tests have been found in some of these cases.[10, 11]

Dr. Kenneth W. Smith[10] in collaboration with Dr. Milton Duncan (1958) found 17 out of 464 employees working in a diatomite plant who had coalescent pulmonary lesions and 11, or 65 per cent of these had negative tuberculin tests (first, intermediate, and second strength). However, this percentage is somewhat lower than the percentage (77 per cent) of negative reactors in the entire group of 464 employees studied. It should also be noted that this high incidence of negative reactors appears to be characteristic of the general population in the same area.

Consideration should also be given to the unique pathological disturbance which is caused by the large amount of amorphous silica even though associated with a much smaller amount of crystalline silica. This disturbance in the form of diffuse mural thickening and consequent alveolar stasis will inhibit the clearing of the fibrogenic silica from most of the air spaces and its focalization into nodules.

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The same factors would thus favor the development of the more widespread and diffuse fibrosis observed in the cases of flux-calcined diatomite dust exposure.

Sclerosis of pulmonary vessels may be widespread because of their proximity to extensive inflammatory foci and possibly also because the vascular walls may be infiltrated by dust. This vascular sclerosis plus the reduction in the total pulmonary capillary bed by the interstitial pneumonitis and by the associated emphysema may cause pulmonary hypertension and cor pulmonale.

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