7

Characteristics and Etiology of Parenchymal Asbestosis

DEFINITION

In 1867 Zenker introduced the generic term "pneumonokoniosis" to embrace essentially similar forms of pulmonary disease caused by the inhalation of dust: "It will then be necessary to embrace under a single title these essentially identical forms of disease . . . the name pneumonokoniosis (from κ, ο, ν, ι, σ, dust) recommends itself. One would then require to distinguish the individual forms as pneumonokoniosis anthracotica, siderotica, etc. (or just briefly as anthracosis, siderosis)." (Meikeljohn's translation, 504). The term was later shortened and anglicized to "pneumoconiosis." Cooke was apparently the first to use the term "asbestosis" in the second of his 1927 papers (157)—in his 1924 paper he referred only to "fibrosis of the lungs due to the inhalation of asbestos dust (156)," and in the earlier of his 1927 papers (159) to "pneumokoniosis due to asbestos dust."

Since Zenker was led to the definition from an examination of lungs, the usual practice of applying the term "asbestosis" only to pulmonary effects seems justifiable. Emphasis on changes in the lung parenchyma is implied in the 1948 (United Kingdom) "Statutory Instrument No. 1371," in which pneumoconiosis is defined as "fibrosis of the lungs due to silica dust, asbestos dust, or other dust, and includes the condition of the lungs known as dust reticulation but does not include byssinosis (281)." Lanza quotes the definition of the (United States) "1935 Memorandum on Industrial Diseases of Silicosis and Asbestosis"—

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"diseases of the lungs produced as a result of the inhalation of asbestos dust (440)."

In these definitions pleural changes are not mentioned or are implicitly treated as complications. By 1970 Mackenzie and Harries were moved to state that, although the progressive interstitial fibrosis of the lung due to inhalation of asbestos fibers is often, but not always, accompanied by pleural fibrosis or pleural calcification, they proposed to restrict the diagnosis to those cases which exhibit clinical, radiological, and physiological evidence of pulmonary fibrosis (471).

The Working Group on the Definition of Pneumoconioses of the 4th International Pneumoconiosis Conference of the International Labour Office (ILO), meeting at Bucharest in 1971, defined pneumoconiosis as "the accumulation of dust in the lungs and the tissue reaction to its presence (800)." They divided the pneumoconioses into two groups: the noncollagenous as produced by tin and by barium sulfate and the collagenous as produced by silica and asbestos. Collagenous pneumoconiosis they characterized by (1) permanent alteration or destruction of alveolar architecture, (2) collagenous stromal reaction of moderate to maximal degree, and (3) permanent scarring of the lung. Again, no mention was made of pleural involvement.

For reasons set out in the preceding chapter (Chapter 6), we will use the term *parenchymal asbestosis* for those changes occurring in the substance of the lung as a consequence of exposure to asbestos dust exclusive of any pleural, mesotheliomatous, or carcinomatous changes that may be present and exclusive also of any changes in organs other than the lung that might result from exposure to asbestos. These will be considered separately in subsequent chapters. We will, however, use the term "asbestosis" without any preceding qualification for the combined parenchymal and pleural changes that constitute the bulk of the cases seen in practice, as will be shown in Chapter 9.

PATHOLOGY

Parenchymal asbestosis, as usually seen in human lungs that are submitted for pathological examination, may be described as a diffuse interstitial fibrosis. In this stage the pathological picture has few features to distinguish it from that seen in interstitial fibrosis of other etiology such as that of possible viral origin, collagen disease, or the so-called "idiopathic" variety. The only pathological finding that is specific is the presence of asbestos fibers, some of which have been converted into asbestos bodies, and even these if few in number may be

of peripheral significance. However, even though other etiologic agents, known or unknown, may produce very similar tissue changes, especially in the more advanced stages of the disease, experimental and human studies have delineated a rather characteristic process and succession of appearances.

Before we consider the macro- and microscopic appearance of the lungs in well-developed asbestosis, a brief account of the developmental process as presently conceived may be helpful.

For initial pathological changes resulting from exposure to asbestos dust we have to heavily rely on the results of experiments with animals exposed to dust by inhalation or by intratracheal injection. Unfortunately, we do not yet have an experimental animal that reacts to asbestos dust in quite the same way as does man. In 1951 Vorwald, one of the earlier experimenters, complained that while guinea pigs showed definite fibrosis and asbestos bodies, rats reacted with fibrosis but produced no asbestos bodies, mice gave bodies but no fibrosis, cats yielded slight fibrosis but no bodies, and rabbits gave very little response at all (761). Later experience has more or less borne this out, but hamsters have been found to react somewhat like the guinea pig and man, and perhaps not too much attention should be paid to differences in the formation of asbestos bodies which, although a striking and potentially protective phenomenon, are something of a side issue insofar as the disabling pathological process is concerned. Many experimenters have used dosages far more intense than those to which man is usually exposed, or intratracheal injections, which have a high degree of artificiality although useful for preliminary studies. Nevertheless, from the various experimental studies, and particularly from the very carefully designed and executed investigations recently reported by Wagner and his colleagues, and with support from occasional examinations of material from persons with recent and mild exposure, we can piece together the events that probably occur during the early stages of the disease in man (171,298,344,346,728,773).

The initial lesion occurs with the lodgement of asbestos fibers in the alveoli arising directly from the respiratory bronchioles. An aggregation of macrophages and red cells around the fibers is soon enmeshed in a network of reticulin fibers. Cellular degeneration takes place and the reticulin fibers are gradually replaced by collagen with obliteration of the alveoli. To quote Wagner, "the primary lesion is, therefore, a focal plastering on of material from within the lumen of the respiratory bronchiole and not an interstitial fibrosis (766)."

In the next phase, fibroblasts around the periphery of the lesion carry the collagen fibers in continuity into alveolar ducts and atria with an

eventual linkage of individual units (Wagner) but a sparing of the peripheral portion of the acini. A so-called "pleural drift" is mentioned by a few writers to indicate a passage of asbestos fibers to the submesothelial connective tissue, where a fibrous reaction occurs (440,523). Visceral pleural and subpleural fibrosis of at least some degree is frequent, and although some authors doubt whether asbestos bodies are really present in this location, fibers have been shown to be present (379). Thomson attributes the passage of fibers to the periphery and to the lower lobes to the effect of respiratory movements, aided in the latter case by gravity (738). With the development of these changes a diffuse interstitial fibrosis is established.

In the course of the process, asbestos bodies are usually formed, and these serve to indicate the most probable cause of the fibrosis. They were, in fact, among the features that captured Cooke's attention in 1927–1929 and indicated that asbestosis was probably a distinct entity (157,158). The description of asbestos bodies given by the earlier investigators is still adequate although a lot more has been learned about their life history since then; this will be taken up in Chapter 16. At the core of the asbestos body lies an asbestos fiber which could be any one of the types described in Chapter 2. Surrounding the fiber is a coating that consists largely of mucoprotein and contains iron probably derived originally from hemoglobin. This coating gives the body a golden-brown appearance and the contained iron gives a prussian blue reaction with ferrocyanide. The coating may have a fairly uniform appearance, be corrugated, or be broken up into beads or segments with more or less exposed core in between. The core may project from one or both ends. As seen by light microscopy, the bodies vary in length from the barely visible up to 70 μm or more, and in thickness up to 25 μm. (With electron microscopy, much smaller bodies may be seen.) While most of the bodies may be fairly straight, they can be curved, bent at an angle, or reduced to a comma form. While some may be found lying in alveolar or bronchiolar spaces, most are imbedded in tissue with various degrees of accompanying fibrosis. For the most part, they may appear to lie free in extracellular positions, but some may be seen partially or completely surrounded by giant cells or macrophage cells, or even lying within a single cell. The intracellular situation is more commonly seen with the smaller bodies visible by electron microscopy. Various techniques have been devised for freeing the bodies from tissue and of concentrating them for better visualization or for quantitation (57). They can be easily found in juice squeezed from the basal portion of cut, fresh lung. While their presence in any quantity is strongly suggestive of asbestos being the cause of any accompanying fibrosis, a small

number may be found in the lungs of persons with minimal exposure and no significant degree of pulmonary change. They may be found in other lymphoid organs, such as the lymph nodes and, occasionally, the spleen, and they frequently appear in the sputum. Fibers other than asbestos can provide a core on which similar coatings can develop, and care has to be taken to distinguish these from true asbestos bodies, which can usually be done by electron probe techniques (Chapter 4). The generic term "ferruginous body" has been proposed to include as well those instances where the nature of the core is unknown or can be shown to be of a nonasbestos nature (297,310). (Color Plates 1b, 1c)

Macroscopic Appearance of the Lung

Initially, the lungs appear of normal size. As fibrosis affects the lower lobes, overaeration of the upper lobes may give them the appearance of being large. The only gross evidence of the early process may be stiffening of the subpleural zone of the lower lobes as felt by palpation; a section of the parenchyma may show no visible change. As fibrosis progresses, the stiffening becomes more diffuse, especially in the lower lobes where an irregular, relatively fine, grayish mottling may be seen. The pleural margins stand out clearly because of the subpleural fibrosis which extends into the interlobar septa (568). At a later stage there is a network of fibrosis, roughly coincident with the pulmonary lobules. In the lower lobes this becomes more evident underneath the diaphragmatic and posterolateral visceral pleura to a depth of 1–2 cm from which it spreads into the depths of the lung. With progress of the disease, areas of fibrosis become confluent. Engorgement of the residual parenchyma provides a deep red background to the blue-black polygonal fibrotic areas (Plate 7-1).

As fibrosis becomes more extensive and confluent, the lungs shrink to subnormal size, although they may be relatively heavy. Descriptions of the later developments vary. Some authors, for example, refer to emphysematous and bronchiectatic changes, while others minimize them. It is possible that some of the changes are due to the operation of other variable factors such as smoking, chronic bronchitis, infection, and neoplastic changes. The majority opinion seems to be that emphysema is not an early or significant process in asbestosis, and that bronchiectasis and bronchiolectasis are not grossly striking features (568). Ennis, however, is of the opinion that pathologists impressed by the fibrosis may gloss over the presence of bronchiectasis (226). Cysts, 1–3 mm in diameter, may ultimately make their appearance between fibrotic areas, with the production of the so-called "honeycomb" lung.



Plates 7-1a,b. Gough sections of lungs showing extensive fibrosis with "honeycomb" development in lower lobes.

but according to Hourihane and McCaughey it is rarely extensive (356) (Plate 7-1).

Massive fibrotic areas are occasionally noted in the absence of any apparent evidence of silicotic or tuberculous processes. The upper lobes may be affected without much lower lobe involvement (292). Necrotic nodules associated with rheumatoid or serum rheumatoid factor have been described (568).

Various pathologists and experimenters have found it necessary to devise some scheme for grading the severity of the pathological response observed. The International Agency for Research on Cancer proposed at its 1964 meeting that one be devised for general use, taking into account both the severity of the fibrosis and the amount of tissue involved (715). Hinson *et al.* reported on such a scheme at the 1972 meeting (336) in which the following grades would appear:

Extent

A. None
B. Where less than 25% of the lung substance is involved
C. Where 25–50% of the lung is affected
D. Where more than 50% of the lung is diseased

Severity

0. None
1. The lesions consist of a slight focal fibrosis around respiratory bronchioles associated with the presence of asbestos bodies
2. The lesions are confined to respiratory bronchioles of scattered acini. Fibrosis extends to alveolar ducts and atria as well as to the walls of adjacent air sacs
3. There is a further increase and condensation of the peribronchiolar fibrosis with early widespread interstitial fibrosis
4. Few alveoli are recognizable in the widespread diffuse fibrosis; bronchioli are distorted

Other features: Symbols are provided to note the presence of certain other changes

bl	Bronchiolectasis
br	Bronchiectasis
ca	Tumor
mf	Massive fibrosis
pq	Pleural plaque
pt	Pleural thickening
tb	Tuberculosis

Microscopic Picture

For the accurate categorization of asbestosis, as suggested by the above scheme, it is essential that at least one tissue block be examined from each lobe. Where there are solid areas of fibrosis, the elastic skeleton of the alveoli can still be demonstrated. Residual, essentially normal alveoli persist especially in the upper lobes when fibrosis is quite extensive in the lower lobes. Macrophages may be clumped but unattached in alveoli or alveolar ducts in these areas. Alveoli adjacent to those undergoing obliteration show fibrosis in their walls, although their form is still apparent. Alveoli adjacent to or entrapped within areas of fibrosis may dilate and the epithelium may undergo cuboidal metaplasia or a proliferation of type 2 pneumocytes. It has recently been shown that these cells contain cytoplasmic hyaline material identical with Mallory's hyaline material as seen in the liver of alcoholic hepatitis (425). This change has been seen in the lungs only in asbestosis; it is not seen in those from cases of alcoholism.

As in other fibrosing processes in the lung, there is a thickening of the wall of small vessels, although Gloyne regarded vascular sclerosis as relatively unimportant (278). Scansetti and Rubino believe that the alveolar–capillary block that is seen in asbestosis is a result, not only of vascular sclerosis, but also of extensive obliteration of the pulmonary capillary bed, which in turn leads to the condition of cor pulmonale (648).

Apart from occasional references to bronchiectasis, bronchiolar distortion, and bronchiolectasis, there seems to be little change in the small airways, and except for their initial role as the collecting point for deposited asbestos fibers, the respiratory bronchioles become involved only in secondary fashion in the spreading diffuse interstitial fibrosis.

CLINICAL CHARACTERISTICS

The account given here is derived from the extensive literature, which has been reviewed by Smither (699), Elmes (215), Wright (803,804), Harries (317), and Leathart (444), and for older material by Roemheld *et al.* (618) combined with the information acquired in twenty years of experience at Mount Sinai. Specific references will be given only where necessary to illustrate a particular aspect.

History and Physical Examination

The presenting symptoms vary with the stage of the disease and also with the rapidity of development. The most common initial complaint is that of dyspnea on exertion, becoming more noticeable with time, and not specifically related to respiratory infection or to the weather. British writers, in fact, aptly refer to parenchymal asbestosis as being a "monosymptomatic" disease. Cough is commonly reported, especially in the morning, but not marked at first and commonly without much sputum. However, we have found cough to be prominent only in those patients who are cigarette smokers; the development of cough in a nonsmoking asbestos worker raises a suspicion of infection or carcinoma.

In the less extensive and uncomplicated cases there is usually not much complaint of pain, but there may be a variable feeling of tightness in the chest. When pain is present, it is usually located over the lower chest. It needs to be distinguished from pain due to other causes, such as that from heavy manual labor. It could be due to pleural changes, and when localized and persistent it points to the probability of underlying malignant changes.

In the older literature there are accounts of debility, sometimes marked, and of nervous depression often suggesting neurasthenia (21,162,560); these features are not common in today's patients. Anorexia and cachexia may be present and are occasionally marked, particularly in the terminal phases of pulmonary insufficiency (204,213,407,560). Lists of the frequency with which the various symptoms appear vary with the author, the date of the report, and the population reviewed. The individual physician may find almost any combination.

The taking of a good occupational history is important, not only to the diagnosis, but often to compensation entitlement as well (673). Those patients who have had substantial periods of employment involving overt exposure to asbestos will usually give the relevant information readily when questioned, particularly now that the hazards of this type of work are widely known. But those whose exposure was not so explicit, or who were exposed for relatively short periods of time in the past, may not volunteer the information unless carefully questioned; they may even have forgotten about it. Careful exploration of the patient's occupational history is essential, and the possibility of neighborhood or family exposure (to be discussed later) has to be borne in mind.

The most distinctive sign to be found on physical examination is the presence of fine dry rales at the base of one or both lungs, sometimes appearing first in the axillary basal region and then spreading to other parts. They may sometimes be heard over the anterior axillary line, lingula, or right middle lobe. The rales are persistent, nonmusical, explosive sounds (also described as crepitations or crackles), that are not abolished by deep breathing or coughing, and are present throughout or appear at the end of inspiration. In contradistinction to tuberculosis, the fine rales of asbestosis are much less common at the apices or in the subclavicular region, or if present they are abolished by turning the patient first to one side and then the other. Pleural rub, by contrast, is usually loud, unilateral, and heard only over a small area of chest wall. Coarse bronchial rales or rhonchi may be heard as well if there is some superimposed infection or bronchitis, as in smoker's lung. The wheezing commonly heard in cases of silocosis or coal workers' pneumoconiosis is not heard in asbestosis. Breath sounds may be diminished. There are seldom indications of any massive emphysema, although chest expansion is often limited. The asbestotic lungs are small and not distended as in emphysema. Hyperpnea or tachypnea may be present and the pulse rate may be raised.

As the disease progresses, other signs may be added. Finger clubbing, when it occurs, involves increased curvature of the nails in both axes, increased springiness of the nails on their beds, and hyperemia of the nail bed; later, there may be hypertrophy of the terminal phalanx. Attempts have been made to render the phenomenon quantifiable by measurement of the hyponychial angle, but this procedure requires further study (317). While clubbing is seen fairly commonly in chronic

respiratory disease, among the pneumoconioses it is not commonly seen in cases of asbestosis. Cyanosis appears when a certain concentration of reduced hemoglobin is present in the superficial capillaries and thus indicates an interference with oxygen acquisition in advanced pulmonary disease. This may be due to the interplay of two factors: interference with transfer of oxygen across the alveolar–capillary membrane and the presence of intrapulmonary arteriovenous shunts. The functional significance of cyanosis is increased if the patient is also anemic. In clinical practice there are many instances where cyanosis is not accompanied by shortness of breath.

The pulmonary pressure may be raised and the secondary pulmonary cardiac sound accentuated at an early stage of the disease and as fibrosis imposes resistance to pulmonary circulation. Few changes are seen in the EKG. There may be some evidence of right ventricular hypertrophy, but the EKG is relatively insensitive to the lesser degrees of hypertrophy. There may be some shift of the P wave axis to the right if the element of obstructive disease is marked. The interstitial fibrotic element, on the other hand, does not affect the pattern (127).

Other clinical manifestations that may occur will be considered in Chapter 9 in connection with diagnosis or with clinical course and complications.

Pulmonary Function

A decline in pulmonary function very often makes it appearance before significant changes can be seen in the chest radiograph. It may be found in the course of routine periodic medical examination of exposed persons before other signs or even symptoms appear.

As was seen in considering the pathological changes in exposed persons, two parenchymal processes tend to be provoked by asbestos dust. The interstitial thickening and fibrosis, particularly in the alveolar walls, progressively restricts expansion and is thus often referred to as the "restrictive" element. It may also interfere with gas exchange. Peribronchiolar fibrosis, on the other hand, produces a degree of obstructive small airway disease and is thus termed the "obstructive" element (189). In general, the restrictive element is by far the more evident and more important (68,375).

We have found that total lung volume is nearly always reduced and that the vital capacity is lowered at an early stage in most cases (58–60). The reduction in both increases as the disease progresses (Fig. 7-1A). Maximum breathing capacity, however, is generally fairly well maintained, with the individual compensating for the diminished volume of each breath by more rapid breathing. He is thus able to continue

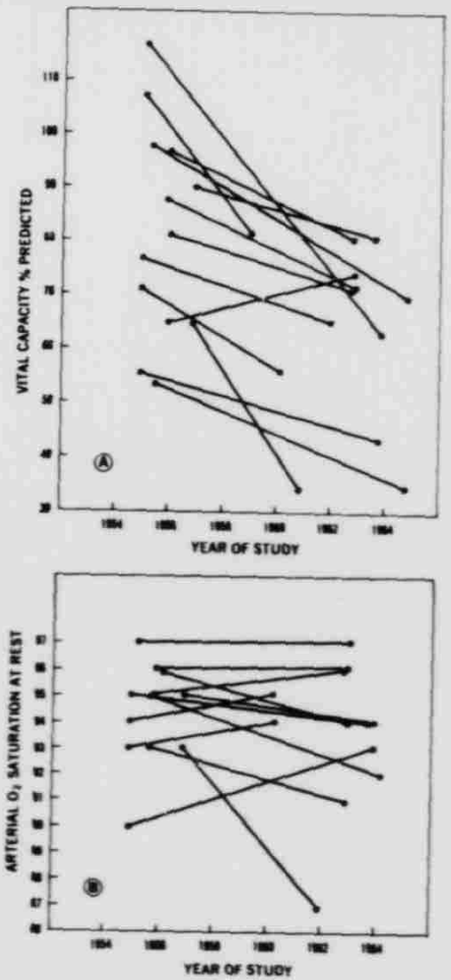


Fig. 7-1. Variation in pulmonary function with progress of parenchymal asbestosis. A, vital capacity; B, oxygen saturation at rest (58). Reproduced with the kind permission of the New York Academy of Sciences.

TABLE 7-1

Reported Lung Function Measurements in Asbestosis (68)[a]

Reference	n		Lung function profile[b]					
	Total	No. classified	Restrictive	Alveolo-capillary block	Obstructive	Mixed	Normal	Other disease present
Bastenier *et al.*, 1955	9	9	2		2	5		
Gernez-Rieux *et al.*, 1954	3	3	2		1			
Gaffuri and Berra, 1957	30	29	8		8	12	1	
Marks *et al.*, 1957	1	1				1		
Read and Williams, 1959	22	22	13		9			
Williams and Hugh-Jones, 1960	21	18	4	1	7	1	2	3
Heard and Williams, 1961	6	6	2			3		1
Bader *et al.*, 1961	17	17	6	6	1	4		
Thomson *et al.*, 1961	39	39	13	6	4	12		4
Bollinelli *et al.*, 1963	1	1	1				6	
De Rosa *et al.*, 1964	85	42	28		5	3		
Bjure *et al.*, 1964	8	8	5		2	1		
Sartorelli *et al.*, 1965	18	16	5		11			
Vaerenberg, 1964	11	11	9		2			
Vecchione *et al.*, 1964	16	16	14		2			
Pellet *et al.*, 1964	28	24	1	1	7	10		5
Kleinfeld *et al.*, 1966	21	21	11	1	1	8		
Hany *et al.*, 1967	8	8	1			5		2
Poggi and Carosi, 1968	17	14	1		8	2		3
	361	305	126	15	70	67	9	18

[a] With kind permission of M. Becklake and the International Agency for Research on Cancer.

[b] The following criteria were used for classification:

Restrictive profile: RV and total lung capacity below 90% of expected value and FEV, ≥ 70% of FVC.

Obstructive profile: RV 110% or more above expected value and FEV, less 70% of FVC.

Alveolo-capillary block: RV and FEV, within 10% of expected value and evidence of impaired gas diffusion from either reduction in D_L, reduced arterial O_2 saturation (SaO_2), or increased A−a O_2 tension differences (Marks *et al.*, 1957).

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accustomed physical work in spite of the dyspnea experienced. Indices of air velocity in the respiratory passages increase with the hyperventilation required to overcome declining functional ability. Increase in residual volumes may not be marked, particularly where the obstructive element is small. It has been reported that the forced expiratory volume in one second (FEV_1) tends to be reduced, as well as the vital capacity in proportion to the fibrosis present, but with differing relationships. (Smoking habits, however, were generally not given.) In the absence of obstruction, the FEV_1 may be low in relation to the predicted vital capacity, but not in relation to the patient's own vital capacity. When obstruction is present, however, the FEV_1 may be low in relation to both. Compliance is reduced in parallel with the vital capacity as the disease progresses; the reduction may appear before radiological changes are seen (205,307,375); some consider it the most valuable single measure of affection in asbestosis (495) but still others find reduction of vital capacity more reliable (416). (For further discussion, see Chapter 13.)

Reduction of the CO diffusion capacity is often the first detectable abnormality, coupled with some increase in the alveolar-arterial oxygen gradient. Oxygen desaturation of the arterial blood may not, however, be great at rest, and the deficit may not advance rapidly with time (Fig 7–1B). The desaturation may become more marked on exercise. Arterial pCO_2 and pH are little affected; the increased ventilation induced by the difficulty of meeting exercise demands is apparently sufficient to take care of any impedance to the diffusion of CO_2 through the thickened alveolar wall.

Experience with alterations of pulmonary function in parenchymal asbestos is not always uniform, however. Numerous variables are involved and there is some disagreement among authors on the frequency with which the various signs and symptoms, including impairment of pulmonary function, may appear or on the sequence with which they appear as the disease develops. Cigarette smoking has a particular effect upon lung function in asbestosis (254). Becklake gives a fairly extensive analysis of changes reported by various authors (68). Some of the comparisons that she makes are reproduced as Table 7–1. In a study of pulmonary ventilation using radioactive xenon in 14 pipe laggers with more than 20 years exposure, Stanley reports finding that emptying of the lower lobes in 10 was faster than in the middle zones at first, but slower later in expiration (711). In two of the workers the emptying was slower in the lower lobes throughout. There was no restrictive or gas transfer defect, but eight had mild airways obstruction. The abnormalities were not related to smoking.

Radiography

In contrast with the state of affairs in silicosis, the early changes in the lung parenchyma with asbestosis, and particularly those in the interstitial tissue, are too diffuse and fine to produce radiographic shadows. As a result, the changes may be difficult to recognize until the disease is fairly well advanced. Alterations in pulmonary function may be found several years before definitive radiographic changes appear and even symptoms may sometimes precede radiographic evidence by a considerable margin.

The earliest change to be seen in the radiograph is usually a very fine reticulation over the lower two-thirds of the lung fields, although an occasional case may be seen with upper lobe dominance. When the pulmonary fibrosis is accompanied by some pleural change, it may give what is often referred to as a "ground glass" appearance (Plate 7–2g). The reticulation is seen with equal frequency on both sides (Plate 7–2a), but other changes are often more easily seen on the right side. The apices remain lucent, sometimes excessively so, as a result of bullae or from some compensatory emphysema. However, infiltration may occur at the apices late in the disease (Plate 7–2f). Nodules or small opacities may appear as the disease progresses and larger opacities are occasionally seen. The markings tend to be coarser in talcosis than in asbestosis. The extensive opacities characteristic of progressive massive fibrosis (PMF) in silicosis and coal workers' pneumoconiosis are uncommon. A report from South Africa mentions them as fairly common but there is reason to believe that the patients were exposed to silica as well as asbestos (703). Gough described the occurrence of solid fibrotic masses in asbestotic lungs (289); we have seen a few cases where exposure to silica seems not to be responsible.

Hilar markings may occasionally be increased as pulmonary hypertension develops or lymph glands enlarge, but this is much less common than in silicosis or coal workers' pneumoconiosis. They are more likely to appear where talc dust is the cause of the fibrosis (6). The heart outline is frequently described as having a "shaggy" appearance as a result of obscuration of the heart border by interstitial infiltration or pleural adhesions (Plate 7–2b). It is possible that the larger opacities and the shaggy heart are the consequence of the fairly intense exposures that were not uncommon in earlier years. Short, thin, parallel horizontal lines spaced 0.5–2.0 cm apart with an appearance similar to Kerley "B" lines may be seen and the interlobar septum itself may become visible.

The changes so far described have little specificity, except perhaps that of the "shaggy" heart, and would of themselves often leave the

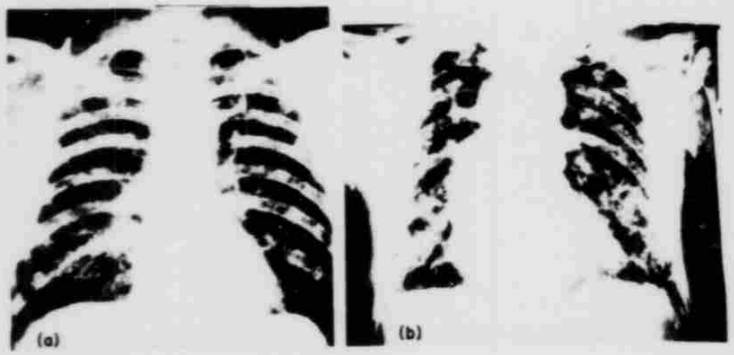


Plate 7–2a. Parenchymal asbestosis (grade 2) fairly evenly distributed.
Plate 7–2b. Parenchymal asbestosis (grade 3), extensive distribution, shaggy heart, thickened interlobar fissure, no calcification seen with Bucky, obliteration of the R. costophrenic angle.

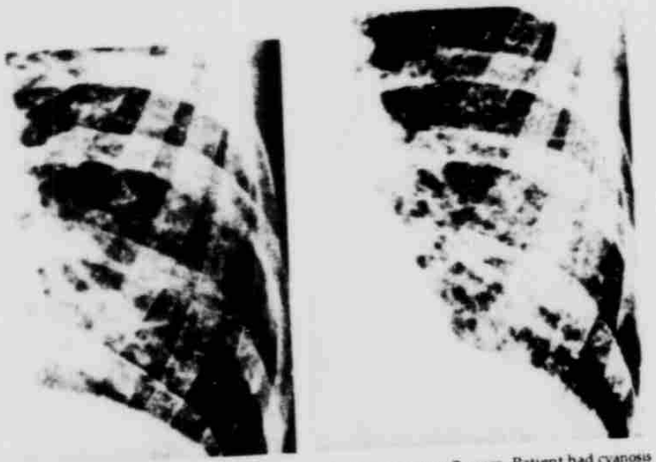
diagnosis in doubt. The more striking and more specific changes that occur in the pleura will be described in the next chapter on Pleural Asbestosis. As the lung volume decreases, the diaphragm tends to rise and this helps to narrow the costophrenic angle. Distortion of the heart shadow may occur in advanced cases.

With regard to technology, Bohlig recommends the use of a high voltage (100–140 kV) and a grid for revealing fibrosis and a low voltage (45–80 kV) for pleural calcification (92). Some of the newer fine grids cast very little shadow but are easily broken and are expensive. 100 mm Film is sometimes used for mass surveys, but early parenchymal changes may be missed. All doubtful cases should certainly be examined with full sized film (94,275,632). Oblique views are useful for providing additional information in doubtful or complex cases. After a series of developmental modifications, a standard (ILO–U/C) classification of radiographic appearances has been developed for use with the pneumoconioses (94,275). The form and details of classification are shown on the record sheet used at Mount Sinai (Fig. 7–2). Other procedures are advocated by some (706).



Plate 7–2c. Progressive asbestosis both lower lobes continuing after retirement in 1960.

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Plates 7–2d,e. Progressive parenchymal asbestosis over 7 years. Patient had cyanosis and clubbing.

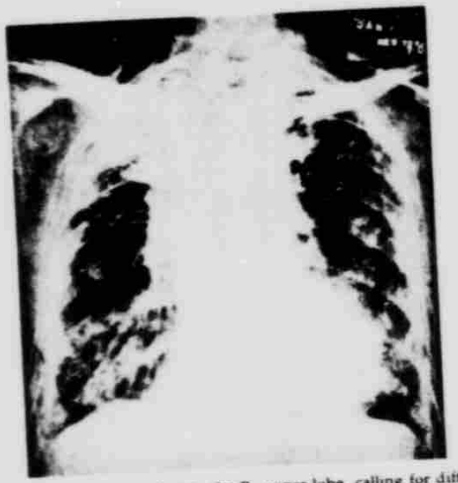


Plate 7–2f. Asbestosis extends into the R. upper lobe, calling for differential diagnosis from tuberculosis.

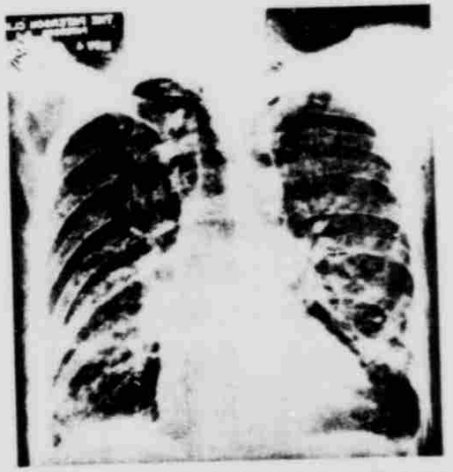


Plate 7–2g. Bilateral parenchymal and pleural asbestosis. Thickening of interlobar fissures, ground glass appearance in lung fields, and calcification on diaphragm.

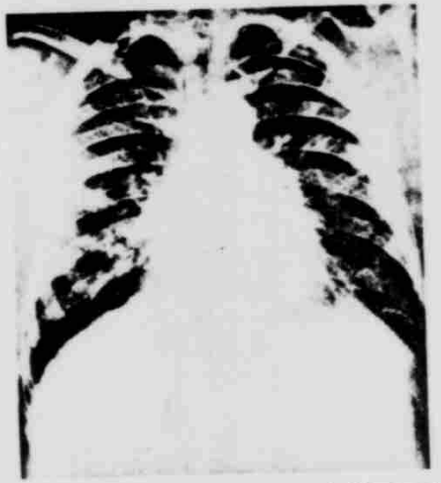


Plate 7–2h. Parenchymal asbestosis with "porcupine" heart appearance.

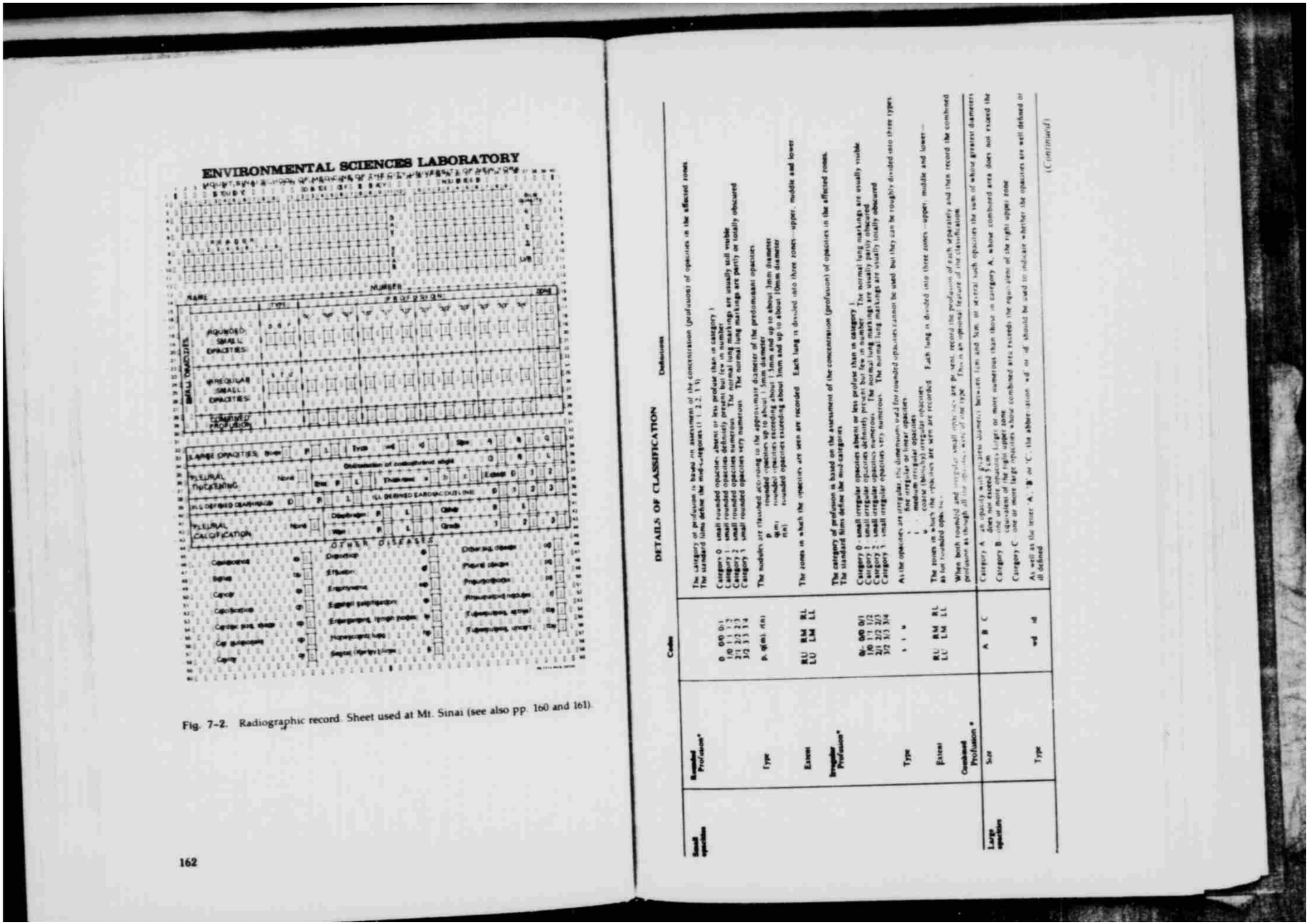


Fig. 7-2. Radiographic record. Sheet used at Mt. Sinai (see also pp. 160 and 161).

DETAILS OF CLASSIFICATION

		Codes	Definitions
Small opacities	**Rounded Profusion***	0 0/0 0/1 1/0 1/1 1/2 2/1 2/2 2/3 3/2 3/3 3/4	The category of profusion is based on assessment of the concentration (profusion) of opacities in the affected zones. The standard films define the mid-categories (1/1, 2/2, 3/3). Category 0 small rounded opacities absent or less profuse than in category 1 Category 1 small rounded opacities definitely present but few in number Category 2 small rounded opacities numerous or abundant but normal lung markings are usually still visible 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 1.5mm diameter q rounded opacities exceeding about 1.5mm and up to about 3mm diameter r rounded opacities exceeding about 3mm and up to about 10mm diameter
	Extent	RU RM RL LU LM LL	The zones in which the opacities are seen are recorded Each lung is divided into three zones—upper, middle and lower
	Irregular Profusion*		The category of profusion is based on the assessment of the concentration (profusion) of opacities in the affected zones. The standard films define the mid-categories
		0- 0/0 0/1 1/0 1/1 1/2 2/1 2/2 2/3 3/2 3/3 3/4	Category 0 small irregular opacities absent or less profuse than in category 1 Category 1 small irregular opacities definitely present but few in number The normal lung markings are usually visible Category 2 small irregular opacities numerous The normal lung markings are usually partly obscured Category 3 small irregular opacities very numerous The normal lung markings are usually totally obscured
	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 (blocking) irregular opacities
	Extent	RU RM RL LU LM LL	The zones in which the opacities are seen are recorded Each lung is divided into three zones—upper, middle and lower— as for rounded opacities
	Combined Profusion*		When both rounded and irregular small opacities are present, record the profusion of each separately and then record the combined profusion as though all the opacities were of one type Thus an optional feature of the classification
Large opacities	Size	A B C	Category A an opacity with greatest diameter between 1cm and 5cm, or several such opacities the sum of whose greatest diameters does not exceed 5cm Category B one or more opacities larger or more numerous than those in category A, whose combined area does not exceed the equivalent of the right upper zone Category C one or more large opacities whose combined area exceeds the equivalent of the right upper zone
	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

(Continued)

Other features			
	Pleural thickening Costophrenic angle	Right Left	Observers of the costophrenic angle as recorded separately from thickening over other sites *A lower limit standard film is provided*
	Walls and diaphragm Site Width	Right Left a b c	Grade a - up to about 5mm thick at the widest part of any shadow Grade b - over about 5mm and up to about 10mm thick at the widest part of any shadow Grade c - over about 10mm thick at the widest part of any shadow
	Extent	0 1 2	Grade 0 - not present or less than grade 1 Grade 1 - definite pleural thickening *in one or more places* such that the total length does not exceed one half of the projection of one lateral chest wall. The standard 45mm defines the lower limit of grade 1 Grade 2 - definite pleural thickening in one or more places such that the total length exceeds one half of the projection of one lateral chest wall
	Diaphragm Ill defined	Right Left	*The lower limit is one third of the affected hemidiaphragm.* A lower limit standard film is provided
	Costho.-cardiac Ill defined (diaphragm) :	0 1 2 3	Grade 0 - not present 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 Site Diaphragm Wall Other Extent	Right Left 0 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 about 3cm* Grade 2 - *one or more areas* of pleural calcification, the sum of whose greatest diameters exceeds about 3cm, but not about 10cm Grade 3 - *one or more areas of pleural calcification*, the sum of whose greatest diameters exceeds about 10cm

SYMBOLS

		the intra-thoracic organs		dust exposure, e.g. surgical or traumatic damage to chest walls, bronchiectasis, etc.
ax	coalescence of small rounded pneumoconiotic opacities	ef	effusion	
		em	marked emphysema	
bu	bullae	es	eggshell calcification of hilar or mediastinal lymph nodes	(pl) pleural plaque (un-calcified)
ca	cancer of lung or pleura			
cn	calcification in small pneumoconiotic opacities	hi	enlargement of hilar or mediastinal lymph nodes	ps pneumothorax
				rl rheumatoid pneumoconiosis (Caplan's syndrome)
co	abnormality of cardiac size or shape	ho	honeycomb lung	tba tuberculosis, probably active
cp	*cor pulmonale*	s	septal (kerley) lines	
cv	cavity	od	other significant disease. This includes *disease not related to*	tbu tuberculosis, activity uncertain
di	marked distortion of			

Synoptic Picture

Because of the many variables that affect the development of parenchymal responses to asbestos dust, and because of the somewhat nebulous nature of many of the early indications of disease, attempts have been made to devise some scheme of scoring the various manifestations and of compounding them into a diagnostic index, but the proposed analyses are best regarded as guides to assessment rather than final indices of effect. Some of the considerations that need to be taken into account in the formation of a final judgment on the total picture have been reviewed by Harries (317). The increased frequency with with various manifestations appear with duration of exposure is indicated in the graphs of Fig. 7–3 prepared by Murphy and Ferris (532).

Exploration

Bronchoscopic appearances may be normal or may reveal nonspecific changes (582). Jacob gives details of bronchograms obtained in two cases (371). Both had severe subjective complaints and abnormal function but only minor radiographic changes. The bronchograms showed distinct shrinking of the bronchial tree in the lower and middle lobes, with bronchitis deformans and delay in reabsorption of the opaque material. There was bunching of the segmental bronchi in the lower lobe with diminution in the angle of subdivision. Russian investigators have reported a high incidence of atrophic changes as seen by endoscopy in the respiratory mucosa of asbestos workers and deformation of the lower segmental and subsegmental bronchi in 28 out of 106 examined (369).

The introduction of fiberoptic bronchoscopy has greatly facilitated the acquisition of peripheral lung specimens by trans-bronchial biopsy, as well as extensive viewing of the airways themselves (734). When placement of the catheter is guided by fluoroscopy, specimens can be taken from most areas of suspected pathology for histological examination and for fiber count if desired. No more than local anesthesia is necessary and patient cooperation is fairly easily obtained. Complications are minimal but the procedure is not entirely without risk (383).

In 1964 W. G. Smith introduced the use of the Jack needle but later abandoned the practice because of surgical complications. Walton and Skeoch, however, reported that they had performed over 200 biopsies with the Jack needle without fatality (774). They describe seven cases in which the diagnosis of asbestosis was confirmed by the presence of fibrosis and asbestos bodies in the material obtained. They too refer

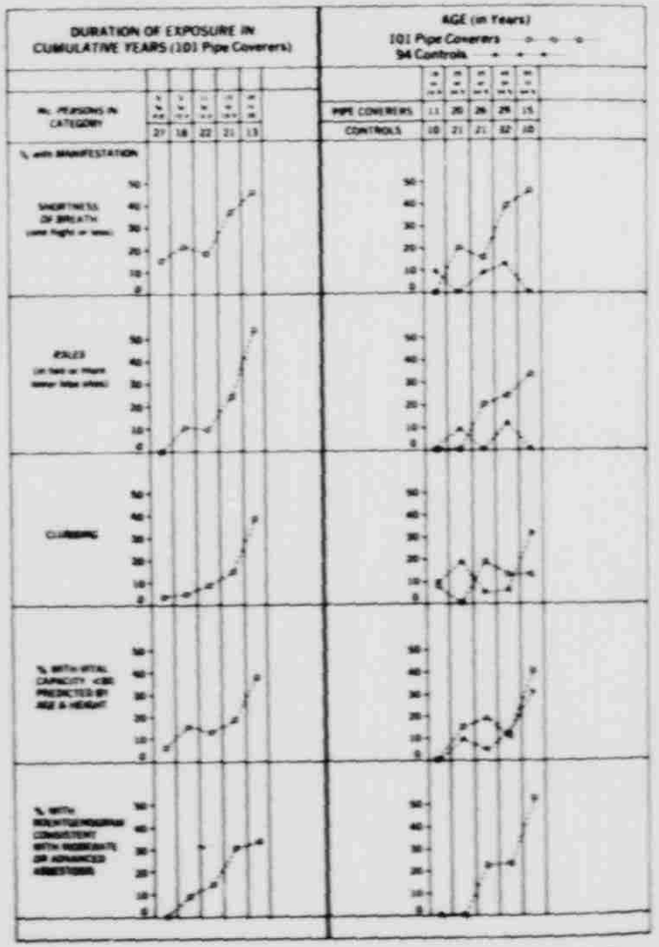


Fig. 7-3. Manifestations of asbestosis vs. duration of exposure and age (532). Reproduced with the kind permission of B. G. Ferris.

to bronchial distortion seen in bronchograms and comment on the tendency of such malformations to retain sputum and promote infection. Mann and Sinha also found the material obtained in 12 cases to confirm the diagnosis of asbestosis in spite of equivocal radiographic changes. However, they encountered many surgical complications, some of them severe (478). We do not recommend this procedure.

Gold and Cuthbert advocate open lung biopsy in cases of doubt and stress the safety of the procedure under good operating conditions (285). It would seem, however, that surgical intervention would not be indicated simply for the purposes of confirming diagnosis unless the matter were critical as in the establishment of a claim for compensation, particularly now that fiberoptic bronchoscopy is available.

ETIOLOGY

From what has been said, it is clear that there is little doubt in anybody's mind today that exposure to asbestos dust can produce pneumoconiotic changes in the lungs that can be characterized as interstitial fibrosis. But this was not always so. In our opening chapter we traced the development of the concept over sixty years from Murray's first report in 1906 to the New York Academy conference in 1964. Even after official recognition of the disease in the 1930's there was considerable reluctance on the part of many, not to say active opposition, to granting the causative relationship. At that time the idea of chronic disease developing many years after commencement of exposure to a putative agent was relatively new. There were no recognized rules for dealing with evidence for or against a suggested association and each party felt free if he so wished to present that portion of the evidence that supported his conclusion (or convenience). In Chapter 6 we presented a set of guidelines, after the style of the well-known Koch's postulates, for guidance in assessing the weight of the evidence when the longterm effects of an agent are under review. It will be useful to apply these guidelines or criteria to the matter of parenchymal asbestosis, both to demonstrate their relevance and to lay the groundwork for consideration of the etiological relationships to other manifestations of asbestos disease on which complete unanimity has not yet been fully achieved. While textbooks usually place considerations of etiology ahead of descriptions of disease, we elected to reverse the order so that the reader, who may not be a physician, will already have been made aware of the clinical features that enter into the analysis.

Association between Exposure and the Syndrome (First Criterion)

For a chronic occupational disease to appear with a frequency compelling recognition, enough persons must have been exposed for a sufficient time, to a sufficient dosage, and in a sufficiently well observed population. With asbestotic diseases, the apparent incidence prior to the 1920's was fairly low; the picture was obscured by the prevalence of tuberculosis in the general population; silicosis dominated men's concepts of industrial lung disease and diagnostic procedures such as radiography were still in a fairly primitive state. As indicated in Chapter 1, such reports as were published did not make the essential etiological correlation.

The association was made clear, however, in the 1930's. Merewether and Price found in England that 95 out of 363 asbestos manufacturing workers examined had evidence of pulmonary fibrosis attributable to asbestos dust and calculated that, on the basis of their sample, one in eight of all workers in the industry would be found to have evidence of fibrosis (510). In January of 1935, Lanza and his colleagues in the United States published the results of a survey of workers actively employed in asbestos fabricating plants showing that, of 126 radiographic examinations, 4 warranted the diagnosis of second degree asbestosis, 63 that of first degree, 39 were doubtful, and 20 were negative (441). In October of the previous year Fulton and his colleagues had issued a preliminary short account of a survey of workers in asbestos textile plants in Pennsylvania, and in October of 1935 they reported that out of 56 such workers, 7 had moderate asbestosis, 7 more had slight changes, 2 were doubtful, and 40 were normal. The positive cases all had 6 or more years of exposure to dust concentrations ranging from an average of 4.64 to 44.26 mppfc* (259). (A distinction was not made in those early years between parenchymal and pleural changes; they usually occurred together at that time, as is indicated by the descriptions then given.)

Dreesen and his colleagues confirmed a similar association with talc in a series of papers published over the period 1933–1935. Among 57 tremolite talc workers, only 3 had radiographic findings within normal limits, 38 showed more markings than usual, and 15 had evidence of first stage pneumoconiosis. Only 18 of the 57 had worked for more than 10 years, and none of these had a normal film (198). (We now know that 10 years is a fairly short time for marked radiographic changes to develop.) In another study, among 33 talc mill workers, 16 had radiographic evidence of pneumoconiosis, 8 of them in second or third stages. Among 13 talc miners, there were 6 cases of stage I pneumoconiosis; there were no such changes in 20 additional workers not exposed (199). Upon radiological examination in 1938 of 447 employees of asbestos textile factories exposed to asbestos, including 69 former employees, they found 16.3% with asbestosis, in spite of a short duration of exposure for most of the men, due to a recent large turnover in those employed (200).

The subsequent years saw increasing numbers of reports on the association between exposure to asbestos and the development of pulmonary fibrosis, but the inquiries increased in depth and introduced consideration of items that pertain to our other criteria.

* For the history of dust counting methods and expression of results, see Chapter 4.

Dose–Response Relationships (Second Criterion)

In applying the toxicological concept of dose–response relationships to environmental situations, it must be admitted that the actual dose is very seldom known; one does not take dust by the measured teaspoon! About the most that one can hope to know is the concentration in the ambient air to which the person was exposed, and that in turn is seldom more than an approximate estimate, as was indicated in Chapter 4 on environmental measurement. Of atmospheric concentrations 30 years ago we know very little beyond the fact that many were very high.

The atmospheric concentration of particles was seldom measured in asbestos industries before the 1930's, and until quite recently the usual practice has been to count all particles above a given size, whether they are asbestos or not, and to base controls on these counts (see Chapters 4,5,19,20). This practice omits measurement of the shorter particles that may be equally if not more important, at least for some features of asbestos disease. It also ignores the bothersome question of what is a particle, the parent large fiber or the numerous offspring into which it can divide.

How much of the ambient dust to which a person is exposed is actually deposited in the lungs is not known with certainty; it probably varies with the individual, his breathing habits, the efficiency of his clearance mechanisms, and his ventilation rate (see Chapter 13). It certainly depends upon particle dimensions which are not always known. Worse still, the techniques of collecting and counting dust particles have changed with the years so that comparisons over a period of time are difficult. These difficulties in estimating the dosage have their counterpart in quantitation of effect. A certain rough quantitation

can be made of radiological changes; first, second, and third stages have already been referred to. But this consititutes a poor effort at measurement. In any case, the radiological changes are late in appearing; they are usually preceded by disturbance of pulmonary function that only recently has been subjected to good measurement (59,68). A rough quantitation can be made of the degree of dyspnea experienced by the patient or of a combination of this and certain early signs (532). At the other end of the clinical spectrum, one can compare the death rate among asbestos workers with that of an unexposed population and examine the causes of death where these can be ascertained with confidence.

Before 1930, conditions in the mines, mills, and factories were largely uncontrolled so that some very heavy exposures occurred. Eyewitnesses speak of being unable to see more than a few feet, for instance, because of the amount of dust in the air. From 1930 on, controls were progressively instituted and conditions generally improved although there were many instances where enforcement of control was lax (114). In looking at the clinical picture today one should think of the ambient conditions 20 or more years ago, not of what now prevails. The disease develops slowly; statistics based upon workers employed for less than ten years will, in general, underestimate the risk. As environmental conditions improve, the development period may very well be lengthened. Some of the statistics cited in the section on association reflect relatively short periods of exposure.

In spite of these marked limitations on the strict application of a dose–response principle, and dependence upon personal judgment rather than hard statistics, a gradation of parenchymal response to probable exposure can be demonstrated in terms of three aspects: intensity, duration, and time elapsed since initial exposure.

Relation of Parenchymal Asbestosis to Intensity of Exposure

Table 7–2, taken from the Merewhether and Price report of 1930 (510), is based on the examination of 363 workers in the textile portion of the British asbestos industry, particularly on those who had been employed for a fairly long period of time. Unfortunately, only 133 were given radiographic examination, so that the incidence of fibrosis was surely underestimated. Even so, the marked effect of the relatively uncontrolled conditions of the earlier period is clearly seen, as is the difference of the effect produced by the less and the more dusty occupations.

Enterline and Weill, studying asbestos–cement workers, found that small radiographic opacities in 908 persons were linked to their total dust exposure as indicated in Table 7–3 (229). It should be noted,

TABLE 7–2

Radiographic Findings in British Textile Workers, 1928–1929 (510)

Years employed	Less dusty group: Number examined	Less dusty group: Number with fibrosis	Less dusty group: Percent incidence	More dusty group: Number examined	More dusty group: Number with fibrosis	More dusty group: Percent incidence
0–4	30	0	0	47	0	0
5–9	40	2	5.0	92	31	33.7
10–14	30	2	6.7	45	22	48.9
15–19	11	4	36.4	14	8	57.1
20 and over	6	4	66.7	13	11	84.6

TABLE 7–3

Percentage Distribution of Radiographic Classification for Small Opacities in Asbestos–Cement Workers (229)[a]

Maximum profusion (UICC Cincinnati classification)	Total dust exposure (million particles per cubic foot-months): ≤250	251–500	501–1000	1001–2000	2001–4000	4001+
0/0 and 0/–	95	93	94	81	70	60
0/1	4	6	4	11	16	17
1/0, 1/1, and 1/2	0	0	2	3	6	13
2/1+	1	1	0	5	8	10
n[b]	(161)	(67)	(105)	(122)	(209)	(231)

[a] With kind permission of P. E. Enterline and the International Agency for Research on Cancer.

[b] n, Number of persons examined.

however, that in this report, as in many others, the measure of dust exposure used is the product of intensity and duration, one that we do not favor for epidemiological studies, since it fails to separate the effects of the two variables.

For one cohort being studied at Mount Sinai, that of 689 asbestos product factory workers who began their first employment prior to January, 1939, and were exposed to fairly high concentrations of dust in the period 1930–1960, the relationship of deaths up to December, 1971, to the relative dustiness is as shown in Table 7–4.

To turn from radiographic findings and mortality data to clinical signs, we may note the recent report by Berry that indicates the prevalence of basal rales in those exposed to fairly high concentrations of dust

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TABLE 7-4

Relationship of Deaths in Textile and Asbestos Workers to Level of Exposure

Deaths	Dust level			
	Minimum	Moderate	High	Very high
Number	86	61	25	24
Percent from asbestos	5	13	20	39

TABLE 7-5

Relationship of Basal Rales to Level of Exposure (74)[a]

Years employed	Number exposed	Mean dust concentration[b] (fibres/cm³)	Cumulative dose (fibre years/cm³)	Number (%) with basal rales
Group 1[c]				
10–	58	10.9	131	1(1.7)
15–	72	11.9	202	1(1.4)
20–	29	13.5	296	4(13.8)
25–	46	14.5	392	8(17.4)
30–	6	15.2	486	1(16.7)
Group 2[c]				
10–	22	3.4	41	0
15–	20	3.6	60	0
20–	10	3.8	84	0
25–	20	4.0	107	1(5.0)
30–	7	4.1	131	0

[a] With kind permission of G. Berry and the International Agency for Research on Cancer.

[b] Fibres/cm³ in terms of membrane filter samples. A "fibre" is a particle longer than 5 μm and having ratio of length to breadth greater than 3:1.

[c] Group 1: men working in fiberizing, carding, and spinning; Group 2: men working in weaving and plaiting.

(over 10 lf_s/ml),* as compared with those with lesser exposures (less than 5 lf_s/ml), and the increased frequency with total exposure in the former group (Table 7-5) (74). Murphy *et al.* found fibrosis 11 times more common among pipe coverers in ship construction, with relatively low average dust levels (5.2 mppcf), than in shipfitters and pipefitters also working in the yards and treated as controls (534).

* lf_s/ml Indicates 10 fibers, 5 μm or more length, as seen by light microscopy. See Chapter 5.

That persons exposed to relatively low exposures may not escape effects is also shown by the examination at Mount Sinai of 210 family contacts of amosite asbestos workers with the results given in Table 7-6. (That asbestos fibers were, in fact, part of the family environment

TABLE 7-6

Radiographic and Clinical Indications of Asbestosis in Members of Workers' Families

	Normal X-ray	Abnormal X-ray	Total
Total examined	296	194	490
Rales*	9(3.0%)	16(8.2%)	25(5.1%)
Cyanosis	1(0.3%)	3(1.5%)	4(0.8%)
Clubbing	2(0.7%)	3(1.5%)	5(1.0%)

* $x^2 = 14.96$, $p < 0.001$.

was demonstrated in Chapter 5.) The dust to which they were subject was presumably brought home on clothes from the work place, supplemented in a small proportion of cases by neighborhood atmospheric contamination from a nearby plant. The abnormal radiographs included some with parenchymal changes and others with pleural changes only. It is noteworthy that the frequency of abnormal radiographs in family contacts ran paripassu with the degree of abnormality seen in those of the workers themselves. Clinical signs of pulmonary asbestosis, however, were uncommon in the family contacts.

In regard to possible effects at the very low end of the scale, namely in those exposed to general community air, the International Agency for Research on Cancer states that "there is at present no evidence of lung damage by asbestos to the general public. The amount of asbestos in the lungs of members of the general public is very small compared to those occupationally exposed. It is greatest where asbestos is mined or worked and lowest in rural areas (274)." It is true, as stated in the report, that there is no evidence of threat to the general public, but the possible prevalence of effects has not been adequately studied; too often environmental scientists have been confronted with the statement that "there is no evidence of any harmful effect" when, in fact, no one had really looked. It may be true that there is no threat, but until it has been demonstrated to be true one cannot close one's eyes to the possibility.

Relation of Parenchymal Asbestosis to Duration of Exposure

Instances have very occasionally been reported in which severe asbestosis has developed after quite a short time (6,574), but apart from

these the disease is seen to develop only slowly, and usually but not necessarily in the course of more or less continuous exposure. In the absence of good measurements of the intensity of exposure, which is generally the case for conditions in past decades, the duration of exposure provides a fairly good measure of dosage, albeit not a linear one.

In Table 7–2 reproduced above from Merewether and Price it is clear, in both the lesser and the more dusty groups, that the incidence of fibrosis increases markedly with the duration of employment. One can also discern the presence of both an upper and a lower limit to this effect. In those with less than four years of exposure, even in the more dusty circumstances, no cases of fibrosis were diagnosed; and when 80% of those in the more dusty group are already affected after 20 years, there are few left who could be added to the roster by still longer experience—saturation is approached.

In 1945 Fleischer *et al.* surveyed men working with asbestos in Massachusetts shipyards and found that 6% of the men with 10 or more years of experience had asbestosis but that none of those with less than 10 years were affected (247). Most of the men had less than 10 years of employment in 1945. Some 20 years later, Ferris *et al.* were able to resurvey some of those who were still employed. The prevalence of asbestosis had increased to 15% by 1967 in spite of the preferential removal of some of the affected by death (244). (By 1972 further deaths had reduced the prevalence in the remainder to 10%.)

In data reported by Hill, Doll, and Knox as of 1965, the mortality from respiratory and cardiovascular disease in 57 workers who had had more than 10 years of exposure by 1933 was 22.0 as against an expected 7.28 based on standard mortality for England and Wales; in those who had less than 10 years of exposure, however, the rate was not then significantly greater than that expected (333). (For later data on the prevalence of lung carcinoma in these workers, see Chapter 12.) In 1967, Murphy and Ferris published the graphs reproduced as Fig. 7–3 showing the increase of five indicators of asbestosis with duration of exposure quite clearly (532).

Data summarized from Sheers and Templeton's 1968 paper, given in Table 7–7, indicates a marked increase in the prevalence of pulmonary disease with the duration of employment in naval dockyards even for those only intermittently subject to overt exposure (677).

That the increase in prevalence of disease with duration of exposure is true for those exposed to anthrophyllite, as well as for those working with other types of asbestos, is indicated by the report of Ahlman *et al.* from which the data of Table 7–8 is taken (3). The number of persons

surveyed is fairly small, but the increase with time seems to be clearly evident.

A cohort of 623 men constituting the membership of the New York–New Jersey metropolitan area insulation workers in January, 1943, with 20 or more years of employment exposure, shows the following occurrence of deaths from asbestosis.

Period	1943–1951	1952–1961	1962–1971
Deaths	1	10	22

And among 17,800 asbestos insulation workers in the United States and Canada on January, 1967, the number of deaths from asbestosis by December, 1971 was 5 out of 12,661 (.04%) with less than 20 years from the beginning of exposure, but 73 out of only 5,119 (1.43%) of those with 20 years or more.

The data of Table 7–9, obtained in studies of 1,117 persons employed as asbestos workers at some time in 1943 or later, and examined in 1963, indicate a general increase in fibrosis with duration of employment.

While many reports show a relationship between the degree of radiological abnormality and duration of exposure, in a careful examination of lungs from 35 cases, Ashcroft and Heppleston were unable to find a corresponding relationship for the degree of histological fibrosis (54). The number of cases examined, however, is too small for a firm conclusion.

TABLE 7–7

Prevalence of Pulmonary Disease in Relation to Asbestos Exposure in British Naval Dockyards (677)[a,b]

Exposure	Years of exposure				
	0–4	5–14	15–24	25 and over	Total
Continuous (workers)	2/10 (20)	4/15 (27)	4/11 (36)	5/6 (80)	15/42 (36)
Intermittent	0/161(0)	5/208(2)	3/148(2)	26/171(15)	34/688(5)
"Insignificant"	0/163(0)	4/212(2)	4/153(3)	6/156(4)	13/684(2)

[a] With kind permission of G. Sheers and the editor and publishers of the *British Medical Journal*.

[b] Ratios indicate the number of cases with pulmonary disease out of the number of workers in that class. Figures in parentheses indicate the corresponding percentages.

TABLE 7-8

Distribution of Asbestosis Cases in Relation to Duration of Exposure to Anthophyllite (3)[a]

Exposure time (years)	Cases of asbestosis	
	Number	% of cohort with same exposure time
< 1	0	0
1- 5	7	1
6-10	20	19
11-15	23	37
16-20	8	25
21-25	21	65
26-30	13	43
> 30	8	53
Unknown	5	38
All	105	8

[a] With kind permission of K. Ahlman and the International Agency for Research on Cancer.

TABLE 7-9

Extent of Radiographic Evidence of Fibrosis in Relation to Duration of Employment in Asbestos Insulation Workers

Duration of employment	Grade of radiographic fibrosis					
	0	±	1+	2+	3+	Total
1 day or less	3	0	4	0	0	7
1- 7 days	4	3	5	1	0	13
1- 4 weeks	5	3	6	1	0	15
1- 3 months	6	6	23	1	0	35
3- 6 months	8	3	19	5	0	35
6-12 months	5	3	15	5	3	31
1- 2 years	7	5	25	8	3	48
2- 5 years	3	8	16	6	3	36
5-14 years	1	0	5	4	2	12

Relation of Parenchymal Asbestosis to Lapse of Time since Initial Exposure

In those who have had continued exposure over the period, the lapse of time since initial exposure and duration of exposure are identical, but where exposure has been interrupted, the effect of time itself can be

investigated; the fibrotic process may continue after exposure ceases. It is also entirely possible that the processes associated with aging can interact with those induced by asbestos.

That the disease may progress apart from continuation of exposure is implied in data concerning 232 asbestos product factory workers employed in 1941–1945 and examined 1969–1970 (Table 7-10) (665). Given time, low or even apparently trivial exposures may result in parenchymal asbestosis.

TABLE 7-10

Extent of Radiographic Evidence of Fibrosis in Relation to Time since Initial Exposure in Asbestos Insulation Workers (665)[a]

Onset of exposure (yr)	No.	Normal (%)	Abnormal (%)	Asbestosis (grade)		
				1	2	3
40+	121	5.8	94.2	35	51	28
30-39	194	12.9	87.1	102	49	18
20-29	77	27.2	72.8	35	17	4
10-19	379	55.9	44.1	158	9	0
0- 9	346	89.6	10.4	36	0	0
	1,117	51.5	48.5	366	126	50

[a] With kind permission of the International Labor Office, Geneva.

In addition to two cases showing asbestosis 10 and 17 years respectively after their last exposure, but with considerable exposure before that, Gold and Cuthbert cite the disease (a) in one person who had had only 1 year of exposure 37 years ago (when exposures tended to be heavy), (b) in a second person who was exposed for 26 months 18 years before, and (c) a third of more classical history who had 9 years of exposure ending 30 years previously (285). Unfortunately, we do not have clinical information on these people in the interim to know whether the fibrotic development advanced to a point and then stopped or whether it continued throughout the period.

Progress after cessation of exposure is also implied to a certain extent for those with "insignificant" exposure cited in the data quoted above from Sheers and Templeton. On the other hand, evidence has been adduced that persons who are removed from exposure when a decrease in lung function has been found, but before there is radiographic evidence of involvement, may retain their remaining lung function better than those who continue with exposure (362). There is probably great variability in the progress of disease after cessation of exposure

with the individual, the degree of affection, and many ancillary circumstances.

Concentration of Agent in Tissues (Third Criterion)

Fibers

As explained in Chapter 4, the demonstration and identification of asbestos fibers in tissues pose some difficulty, particularly as routine measures. The light microscope does not have sufficient resolution to reveal fibers much shorter than 1 μm in length, while the making of counts with the electron microscope takes a great deal of time. Identification, even of chrysotile fibers with their characteristic tubular fibrils, is not easy unless EM techniques are employed. By the time that satisfactory techniques had been developed, the etiologic role of asbestos in the production of fibrosis was more or less accepted so that there was not a great urge to pursue identification in other than doubtful cases. There was, however, considerable interest, as we shall see later (Chapters 10–12), in investigating the relationship of asbestos fibers to certain other disease manifestations, and most of the counting and identification was devoted to those questions.

The demonstration of asbestos fibers in lung tissue, or in sputum, is clear evidence that the person has been exposed to the material but it does not necessarily mean that he is suffering from an asbestos-related disease or, conversely, that any disease present is due to asbestos, although the likelihood of that being so is increased. As the background count of asbestos fibers in the environment rises and spreads with the wellnigh universal use of the material, the mere demonstration of fibers in the lungs acquires diminishing significance, although the increasingly rare instance of the absence of fibers would be strong evidence against a diagnosis of asbestos-related disease. What is needed is a clear demonstration that the counts are considerably higher in the lungs of those persons with fibrosis who are known to have been exposed, but the problem is complicated by the tendency of asbestos fibers, particularly those of chrysotile, to disappear from tissue, perhaps by solubilization in tissue fluids, so that the fibers that one sees are simply those that have survived some clearance process. As mentioned earlier, Ashcroft and Heppleston found a progressive rise in the asbestos fiber content of the lungs of 35 persons with the severity of histological fibrosis during the lesser grades of disease, but no further increase in severely fibrotic cases (53,54). [A]

Le Bouffant comments that fiber counts by electron microscopy on asbestos workers generally give very high intrapulmonary concentrations, frequently from 10–50 × 10^6 particles per gram of dry tissue, but that chrysotile becomes rare as compared with amphiboles (445,447).

The ubiquity of fibers in the lungs of at least one urban population is demonstrated by studies on 3,000 consecutive autopsies on residents of New York City (435). The results with light microscopy and with EM examination of 10 °g of lung from 28 consecutive autopsies are given in Table 7–11.

TABLE 7–11

Concentration of Asbestos Fibers and Fibrils in Lungs of New York City Dwellers (435)*

Fine fibers seen by light microscopy in 175 μm × 1 cm² of lung tissue from 3,000 autopsies				
Number of fibers	0	1–4	1–14	15+
Number of autopsies	1962	865	125	48
% of autopsies	65.4	28.8	4.1	1.6

Fibers and fibrils seen by electron microscopy in 28 autopsies					
Number of fibers and fibrils	< 10	10–50	51–99	100–200	200+
Number of autopsies	4	11	6	4	3

* With kind permission of Unwin Co., publishers of "Inhaled Particles III."

The significance of these findings in urban residents is difficult to assess. We have little information on the distribution in other populations and the amounts are quite small. But even in asbestos workers the quantity seems to range only from 0.6–0.001% of lung weight (63); much smaller amounts could be expected in the lungs of those not occupationally exposed. Similar results have been reported by Pooley *et al.* (581). The demonstration of asbestos fibers in the lung tissue of persons without any history of exposure to asbestos assumes greater significance when interstitial fibrosis is present and leaves open the question of whether in that patient asbestos was or was not responsible for the condition. The application of the term "idiopathic" to such cases simply reflects the difficulty of proceeding from estimates of probability to a diagnostic decision in a particular case (515).

"Asbestos" Bodies

As was mentioned earlier in dealing with the pathology of parenchymal asbestosis, and as will be discussed further in Chapter 16, asbestos fibers can acquire a proteinaceous coating with contained iron in the course of their residence in tissue. As early as 1906 Marchand

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reported finding peculiar bodies staining for iron in the lungs of two patients, but he did not give any history of their association with asbestos (482). In 1914 Fahr reported "crystals," also staining for iron, in the lungs of a woman who had worked in an asbestos factory (240). In 1929 Cooke told of finding "curious bodies" in the lungs of his patient (158). Stewart and Haddow conferred upon them the name of "*asbestosis*" bodies (716) but the term was later changed to "*asbestos*" bodies to avoid the implication that fibrosis was necessarily present as well. From that time on, the occurrence was reported with increasing frequency.

That such bodies can be found in the lungs of persons exposed to asbestos is now well established. To reduce observer variation, which can be quite high, the IARC Working Conference in 1972 recommended a semiquantitative mode of reporting the frequency of occurrence in routine histological specimens; from Class 0 with no asbestos bodies to Class 4 with very many bodies, usually many bodies in each field. But, as with the fibers themselves, asbestos bodies are not necessarily accompanied by any fibrotic process, taken alone they simply indicate exposure (218,440,673,737). There is, of course, an onus upon the investigator to satisfy himself that what he sees are truly asbestos bodies and not similar structures built around some other type of fiber (see Chapter 16). As mentioned earlier in connection with pathology, they have been found by numerous investigators in the lungs of random or successive autopsies on persons, particularly city dwellers, who have died from causes unrelated to asbestos disease (20,34,79,153,250, 269,613,625,755). Montreal, New York, Miami, Paris, Milan, Dresden, Glasgow, and London, to name a few cities only some of which have well developed asbestos industry, have all yielded evidence of this nature. In New York, at least, the frequency of occurrence appears not to have changed between 1934 and 1967, as indicated in Table 7-12, giving the number of asbestos bodies found by light microscopy in ashed tissue sections, each 175 μm × 1 cm². The frequency increased with age, as might be expected, since the protective coating around the fiber favors accumulation.

TABLE 7-12

Frequency of Occurrence of Asbestos Bodies in Lungs of New York City Dwellers, 1934 and 1967[a]

	Age					
Year	0–9	10–29	30–59	60+	Unknown	Total
1934	1/8	2/11	25/40	23/31	3/10	53/100
1967	0/0	3/7	24/41	33/52	—	60/100

[a] Ratios indicate number of autopsies showing asbestos bodies out of the total of autopsies examined in that age group and that year.

Oldham, on the other hand, reports a steady increase in the proportion of asbestos bodies seen in lung tissue from 100 consecutive autopsies in London at ten year intervals from 1936–1966 (559). From zero prevalence in 1936, the percentage had risen to 18.2 in males and 22.2 in females in 1966. The comparative prevalence in different cities in 1967–1969 is given in Table 7-13 taken from the same report. Doniach *et al.* found that the distribution of asbestos bodies in an East London population showed correlation with occupation and location of residence in the neighborhood of asbestos plants (195), but Breedin and Buss report finding ferruginous bodies in 90% of autopsies in both rural and urban dwellers (111).

TABLE 7-13

Frequency of Occurrence of Asbestos Bodies in Lungs of European City Dwellers (559)[a]

	London examinations, 1936–1966					
	No. of cases examined		No. positive		Percentage positive	
Year	M	F	M	F	M	F
1936	82	45	*0*	*0*		
1946	61	39	3	0	4.9	
1956	51	49	8	6	15.7	12.2
1966	55	45	10	10	18.2	22.2

Comparison of frequencies in different cities	
Cities, 1966	Frequency (%)
Finland	38
Glasgow, London Hospital	22–26
Dresden, Belfast, London RPGS, Liverpool	13–17
Dorchester, Nottingham	6–9
Galway	1

[a] With kind permission of P. D. Oldham and the International Agency for Research on Cancer.

On the matter of relationship between the lung content of asbestos bodies and asbestos fibers respectively there is considerable uncertainty. Langer *et al.* found a moderate correlation between the two in the study mentioned above using electron microscopy (435), but Davis and

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Gross were unable to find any in lung sections from Pittsburg and Charleston, South Carolina examined by light microscopy (179). The latter authors reported that the ratio of coated to uncoated fibers ranged from 1:15 to as low as 1:11,000, which is in accordance with other findings to be discussed in Chapter 16 that less than 1:1000 fibers may be converted to asbestos bodies. With such a small proportion of conversions it would indeed be surprising if any correlation could be established.

Asbestos bodies have been found in the nasal sinuses and in other bodily sites such as thyroid, spleen, and kidney indicating their mobility (417). They also appear in the sputum, as do asbestos fibers themselves (693) and attempts have been made to use their appearance as diagnostic of asbestos disease, or their concentration in sputum as an indication of the extent of disease (80,215,350). Indeed, a general relationship between the frequency of occurrence of asbestos bodies in the sputum and exposure to asbestos has been shown (294,693). But for the reasons given above, sputum counts do not seem to be very reliable indicators of the presence of disease or of its severity. In any case, as will be pointed out again in Chapter 16, only a small proportion of fibers are converted into asbestos bodies. They can appear in the sputum soon after initiation of exposure, long before any significant fibrosis can have taken place.

In the face of such ubiquity of asbestos bodies and the difficulty of making accurate counts, attempts to relate the concentration in the lungs to the degree of fibrosis present are not likely to be very successful. It must be remembered, also, that fibers which have been coated have, in effect, been removed from the opportunity of initiating tissue response and represent a sidetracked fraction of the whole. They may get a second chance at action when, as often happens, the asbestos bodies break up.

Animal Experimentation (Fourth Criterion)

From 1931 onward, numerous animals—rats, cats, guinea pigs, hamsters, rabbits, and monkeys—have been exposed experimentally to the inhalation of asbestos dust (171,264,343,345,761), but no experimental animal has yet been found that reacts exactly like man. Unfortunately, also, circumstances of exposure are necessarily different from those under which man is exposed. Concentrations of dust in the test atmosphere are often very high (40 or more mppcf) and sometimes not really comparable in composition (539). The reactions then tend to be of the subacute type and are mainly useful in providing examples of early

tissue responses or for the comparison of the relative reactivity of different types of asbestos. The most satisfactory experiment reported to date is that on rats by Wagner *et al.* in 1974 (773). They used five different kinds of asbestos at concentrations of 10.6–14.1 mg/m³ (ng/liter), for periods up to two years, and obtained asbestotic reactions very similar to those seen in man, except for the formation of asbestos bodies, which can be regarded as something of a side issue. The mean weight of dust retained in the lungs, as shown in Fig. 7–4 reproduced

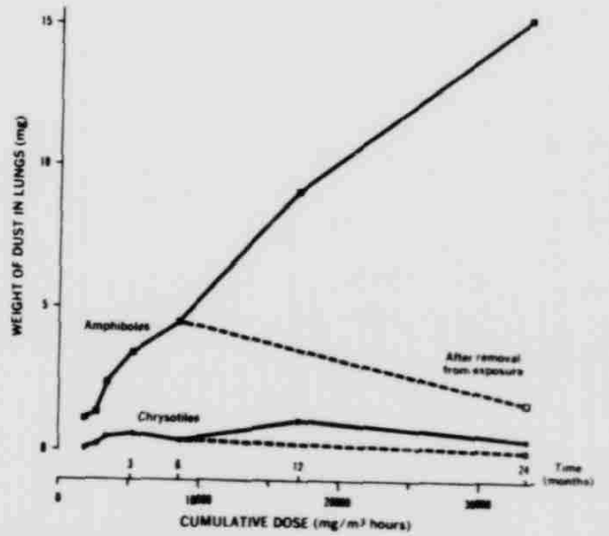


Fig. 7–4. Mean weight of dust in the lungs of rats in relation to cumulative exposure to the inhalation of asbestos (773). Reproduced with the kind permission of J. C. Wagner and the publishers of the *British Journal of Cancer*.

from their paper, reveals a much greater accumulation of amphiboles than of chrysotile, suggesting some kind of clearance mechanism for the latter. The progress of asbestosis during continued exposure and after removal is shown in Fig. 7–5 and Table 7–14, also taken from their paper. It will be seen that all five types of mineral were fibrogenic with perhaps some greater activity by anthophyllite.

Fibers of various sizes, including particles visible only by electron

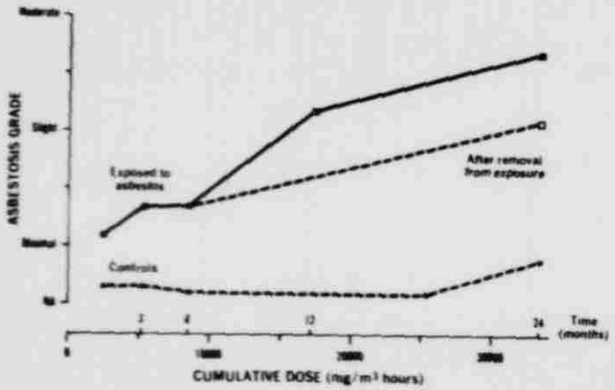


Fig. 7-5. Degree of pulmonary fibrosis in rats in relation to cumulative exposure to the inhalation of asbestos (773). Reproduced with the kind permission of J. C. Wagner and the publishers of the *British Journal of Cancer*.

TABLE 7-14

Development of Pulmonary Fibrosis in Rats in Relation to Cumulative Exposure to Asbestos (773)[a]

Length of exposure	Mean asbestosis scores[b] of sacrificed rats					
				Chrysotile		
	Amosite	Anthophyllite	Crocidolite	Canadian	Rhodesian	Control
8 weeks	2.0	2.0	2.0	2.0	2.7	1.3
3 months	2.5	2.7	2.8	2.7	3.0	1.3
6 months	2.2	3.2	2.6	3.0	2.6	1.2
12 months	4.0	5.2	4.3	4.3	4.3	—
18 months	—	—	—	—	—	1.2
24 months	4.3	6.2	4.8	6.0	5.8	1.8
6 months (after 18 months nonexposure)	3.2	5.0	3.7	5.5	3.7	—

[a] With kind permission of J. C. Wagner and the publishers of the *British Journal of Cancer*.

[b] 1:nil, 2:minimal, 4:slight, 6:moderate, 8:severe.

microscopy, have been found in conjunction with the fibrotic reaction in the lungs of exposed animals. The formation of asbestos bodies has been followed particularly in those animals such as hamsters which are more reactive in this respect. From the etiological point of view, these experiments provide strong supporting evidence of the causal relationship between asbestos and pulmonary fibrosis. More directly relevant, though much fewer in number, are observations on the occurrence of pulmonary fibrosis, resembling that found in man, in animals such as dogs, wild rodents, baboons, and donkeys that have lived near or in asbestos workings (680,777).

Influential Factors (Fifth Criterion)

In asbestos disease, as in any occupational disorder, three types of variability are encountered: variability in the exact nature of the exposure, in the state of the exposed person, and in various circumstances that attended the exposure. Some of the factors that could influence tissue response have been identified.

Variability in the Person Exposed

Variability in host susceptibility to microorganisms has been thoroughly studied and the discipline of immunology has developed to an exciting stage; but, unfortunately, we have very little knowledge of why some persons exposed to fairly high concentrations of asbestos dust develop fibrosis readily while others may live to an advanced age with little impairment (731,802). In 1965 the Mount Sinai investigators reported, for example, that almost 6% of men engaged in insulation work for 40 years or more showed no radiological abnormalities (668). Some investigators have presented evidence that cigarette smoking seems to speed up the process, or at least to increase the disability experienced (306,787); others however, have not been able to find such an association (319). As mentioned earlier, we find that cough becomes a more marked feature in those asbestotic patients who are cigarette smokers but whether this has any effect on the asbestosis itself is not clear. In the early years of the century, when tuberculosis was common, it was reported that exposure to asbestos seemed to increase susceptibility to infection, or at least to more active development of the disease; but doubt has been cast in recent years on the validity of these observations. Respiratory infections are thought by some to increase the rate of fibrotic development in those already affected, but again, more evidence is needed.

Variability in the Dust

To the extent that more fibrogenic dusts such as free silica are included in the incident dust, the effect on exposed persons can be expected to be more severe and and to take on some of the characteristics of the corresponding pneumoconiosis. Insofar as the different types of asbestos are concerned, all seem to be fibrogenic (310,773). Regan *et al.* reported that chrysotile is less fibrogenic than amphiboles on the basis of the relative prevalence of asbestosis in three plants, but they give no data on the intensities or durations of exposure in the three populations (601). Talc, as has been mentioned previously, produces much the same effect as asbestos, but perhaps at somewhat higher dosage (199,295,406). Inasmuch as talc may be highly contaminated with asbestos fibers, the effect is to be expected and cannot be entirely attributed to the fibrous forms of talc mineral. Other silicates have from time to time been incriminated as well. [A]

The matter of particle size has been the subject of considerable controversy. Earlier investigations indicated that only fibers longer than 20 μm were fibrogenic (761) and a recent review suggests that fibrogenicity decreases progressively as fibers are shorter (310). There are, however, some demonstrations to the contrary (345). The matter will be taken up in some detail in Chapter 17, when mechanisms of pathogenicity are being discussed. The contribution of short fibers to responses other than the fibrogenic will also be discussed at that time.

Summary of Etiology

Almost any one of the items cited in support of asbestos being the cause of progressive parenchymal fibrosis in exposed persons, taken alone, might be questioned, but all of the items taken together provide overwhelming evidence for a genuine causative relationship. The conclusiveness of the indictment, in fact, has long been accepted by those familiar with the disease, though not, perhaps, by those more peripherally concerned. Discussion today centers mainly around the question of what could be considered a "safe" dose, as we shall see when we discuss the formulation of standards in Chapter 18. In this matter, the ability of asbestos to evoke pulmonary fibrosis becomes today a subsidiary matter as compared with its ability to produce neoplasms. To a certain extent in this chapter we have been fighting past battles in probing the etiology of parenchymal asbestosis, but the lessons learned will stand us in good stead when we come to discuss the

responsibility of asbestos dust for other manifestations such as pleural asbestosis, mesothelioma, and asbestos-associated carcinoma; matters on which there is less unanimity. We agree with Fondimare and colleagues that "il semble exister une relation effet-dose si l'on s'en tient aux manifestations histo-pathologiques presentees par les subjets d'une part et a la tenure de leurs poumons en corps asbestosiques et fibres d'amiante d'autre part" (250).*

* There seems to exist a dose–effect relationship if one takes into account, on the one hand, the histo-pathologic picture presented by the subjects and, on the other, the concentration of asbestos bodies and asbestos fibers in their lungs.

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