11.7

Asbestosis and Asbestos-Related Pleural Disease

Linda Rosenstock

Asbestos, also known as asbestiform minerals, is a term applied to a group of minerals that are naturally occurring, often magnesium-containing fibrous hydrated silicates. Six fibrous silicates are commonly referred to as asbestos, including the three most common commercial forms: chrysotile, or white asbestos; amosite, or brown asbestos; and crocidolite, or blue asbestos. Although there is some evidence that the biologic potency differs among the various fibers, from the point of view of the clinician, it should be recognized that the three main commercial types have been associated with all of the major malignant and nonmalignant asbestos-related conditions.

The range of health effects from asbestos exposure is protean, including both pulmonary and nonpulmonary malignant and nonmalignant conditions. This section focuses on two major nonmalignant pulmonary sequelae: asbestosis and asbestos-induced pleural disease. Although these two types of outcomes—pleural and parenchymal—have distinct pathologic manifestations, it is helpful to consider them together, both because it is often difficult to distinguish their clinical effects and because although they can occur in isolation, they are commonly present in the same individual because both are dose-dependent outcomes of the same asbestos exposure.

EPIDEMIOLOGY

Worldwide use of asbestos has steadily increased over the past century. Although consumption of asbestos in the United States and other developed countries has declined in the past several decades, global production and use continue to increase. Many of the properties that have made asbestos such an attractive industrial product are responsible for its potency as a hazardous substance—key among them is its environmental persistence. Asbestos is now ubiquitous in the environment in the industrialized world and soon will be so in much of the developing world.

Despite the evidence that began accumulating soon after its widespread use of the myriad health effects attributable to asbestos exposure, detailed information about the population at risk has been sporadic and largely confined to studies of occupational cohorts. Variability in disease prevalence among different populations of workers with comparable cumulative asbestos exposure doses has been repeatedly observed; factors to explain this are likely to include differences in fiber size, type, and distribution as well as individual host susceptibility factors. One recent study (Nicholson et al., 1982) has quantified the number of United States workers occupationally exposed to asbestos from 1940 to 1979. The investigators identified about 19 million workers likely to have had significant occupational exposure during this time period and estimated several hundred thousand deaths among those exposed, primarily due to lung cancer, and to a lesser extent to mesothelioma and other cancers.

The best evidence about the risk for the major nonmalignant sequelae remains those studies based on select groups of exposed workers. There is reasonable evidence that, for asbestosis, there is a strong linear dose-response relationship between exposure and the proportion of the population affected. It is likely that there is some exposure threshold, although none has been demonstrated convincingly, such that individuals with low exposures or even higher exposures for short duration (for example, days to weeks) are not at risk. This pattern is probably different from the relation between exposure and asbestos-related malignancies, in which even low-level or brief exposures confer at least a theoretical increased risk. The strength of the dose-response relationship is not as clear for asbestos-induced pleural disease, but it is likely that also for these outcomes, there is a threshold below which no elevated risk occurs and above which there is an increase in proportion affected with increasing exposure. Asbestos-exposed workers with the highest level of exposures, for example, asbestos insulators, accordingly bear the greatest burden of asbestos-related effects. Among workers certified by medical panels as having asbestosis, life expectancy has been found to be significantly shortened, and most will succumb to an asbestos-related disease (40% dying from lung cancer, 9% from mesothelioma, and 20% from asbestosis).

Among populations of asbestos-exposed workers, prevalence rates of asbestosis and asbestos-related pleural thickening vary with intensity and duration of exposure and latency of disease. For example, even among heavily exposed workers, usually no more than about 50% have radiographic evidence of interstitial fibrosis. But among long-term, older heavily exposed workers, as many as 80% show radiographic evidence of pleural thickening. Prevalence rates for both outcomes are accordingly lower among those with lower expo-

sures as measured by both intensity and duration. Because latency plays such a major role in the radiographic appearance of nonmalignant sequelae—with usually none apparent prior to 20 years from first exposure—the mean age of populations studied is of major significance when considering whether populations have comparable outcomes. Recently reported findings using routine chest x-ray studies obtained in a 1970 United States national examination survey demonstrated that 2.3% of men had occupational pleural thickening, which extrapolated to an estimated 1.3 million individuals with occupationally related asbestos-induced pleural thickening at a time when about 8 million workers were exposed to asbestos. At present, NIOSH estimates between 2 to 2.5 million workers are exposed to asbestos dust.

Nonoccupational environmental asbestos exposures occur but are of less well-established clinical significance. Both pleural and interstitial changes have been demonstrated at a surprisingly high frequency (35% and 17%, respectively) in one study by Anderson et al. (1978) of presumably significantly exposed household contacts of asbestos workers. Population surveys have identified higher rates of pleural abnormalities in locations where asbestos occurs naturally; depending on the setting, the prevalence of asbestos-induced pleural thickening has ranged from 2% to 17% in a number of studies demonstrating this outcome in those persons who were environmentally exposed.

Of interest to the clinician, most series have identified a nonconcordance in individuals between the development of parenchymal versus pleural manifestations of exposure; among those who have been occupationally exposed who have radiographic evidence of interstitial fibrosis, about half will have concomitant pleural thickening and among those with pleural thickening, usually a smaller proportion (less than 30%) will have concomitant interstitial findings.

PATHOLOGY AND PATHOGENESIS

In addition to the pathologic findings associated with pleural and parenchymal fibrosis, evidence of exposure itself can be found in sputum, lung tissue, and bronchoalveolar lavage (BAL). The asbestos body, known also as the ferruginous body, is a brownish club-shaped symmetrically nodular structure that stains for iron because of its high ferritin content. The ferruginous body is nonspecific for the asbestos fiber. These bodies can arise in response to an array of foreign fibers, but those with transparent cores usually are secondary to asbestos. Asbestos bodies are a better reflection of amphibole than chrysotile asbestos lung burden, and they reflect only a small proportion of the total load of asbestos fibers. Those with parenchymal asbestosis have the highest concentration of asbestos fibers in lung (number of fibers per weight of lung tissue); those with pleural plaques have higher numbers of fibers than those without, and those with occupational exposure have higher concentrations than those without, regardless of radiographic or functional manifestations of exposure.

Asbestos fibers are inhaled deep in the lung, exerting their main influence at the level of the respiratory bronchioles and alveoli. Inhaled fibers are long (100 μm or more) and narrow (0.1 to 0.2 μm). It is not understood how fibers actually migrate to the pleura, presumably via the lungs, intercostal lymphatics, or both.

The mechanism of fibrosis is not well established. Asbestos is cytotoxic and reacts with sialic acid on cell membrane glycoproteins. There is some evidence that oxygen-free radicals play a role in the pathogenesis of asbestos-related disease. Studies in animals and humans also support the potential importance of immune-mediated events following asbestos exposure. For example, about 25% of individuals with asbestosis have elevated antinuclear or rheumatoid factors. On the other hand, patients with isolated pleural plaques do not have an increase in antinuclear antibody or rheumatoid factor positivity. Absolute numbers of T lymphocytes and, specifically, T helper cells also have been noted to be increased in BAL in asbestos-exposed individuals and particularly those with pleural abnormalities, but granulocytes have been shown to correlate more closely with fibrosis, a decrease in diffusing capacity, and progessive loss of lung function in patients with asbestosis.

In vitro, asbestos has been found to activate both the alternate and classic complement pathways. It is thought that the release of chemotactic and vasopermeability factors presumably plays some role in the cascade of events, which likely also involves interaction of asbestos with alveolar macrophages, fibroblasts, and lymphocytes. The role of direct mechanical irritation of asbestos fibers in the lungs and pleura also has been theorized to contribute to their pathogenesis.

The macroscopic appearance of asbestosis (used here to refer only to parenchymal asbestos-induced fibrosis) is that of small, firm and brownish lungs, occasionally laced with gray fibrous streaks. Pulmonary fibrosis is linear and involves predominantly the lower lung fields, and honeycombing may be present. Histologically, the parenchymal interstitial fibrosis is similar to that found with an array of causes of diffuse infiltrative lung disease, except that asbestos bodies (and elevated asbestos fiber content) are present. The histologic diagnosis of asbestosis is based on the minimal findings of fibrosis of the walls of the respiratory bronchioles in association with asbestos bodies (Fig. 20). The distribution of fibrosis in early or mild disease is in the subpleural parenchyma; with increasing involvement, the process becomes more centralized.

Fibrosis in the walls of respiratory bronchioles may be the sole manifestation of parenchymal effect and likely represents the early stages of asbestosis. Some investigators believe that these bronchiolar changes are a separate outcome that is unrelated to interstitial fibrosis; however, they are clearly present in workers with significant asbestos exposure and asbestosis and are likely to explain, in part, the airflow obstruction attributable to exposure.

Pleural plaques are discretely elevated gray-white areas of fibrous tissue, usually involving the parietal pleura (specifically, the mid-thoracic chest wall and domes of the diaphragm). Plaques may be smooth or nodular, and round or irregularly shaped. Parietal plaques tend to calcify with time; histologically, there is no difference other than the presence of calcium between noncalcified and calcified plaques, and these sequelae have been collectively referred to as hyaline plaques.

Diffuse pleural thickening results from thickening and fibrosis of the visceral pleura, often with fusion to the parietal

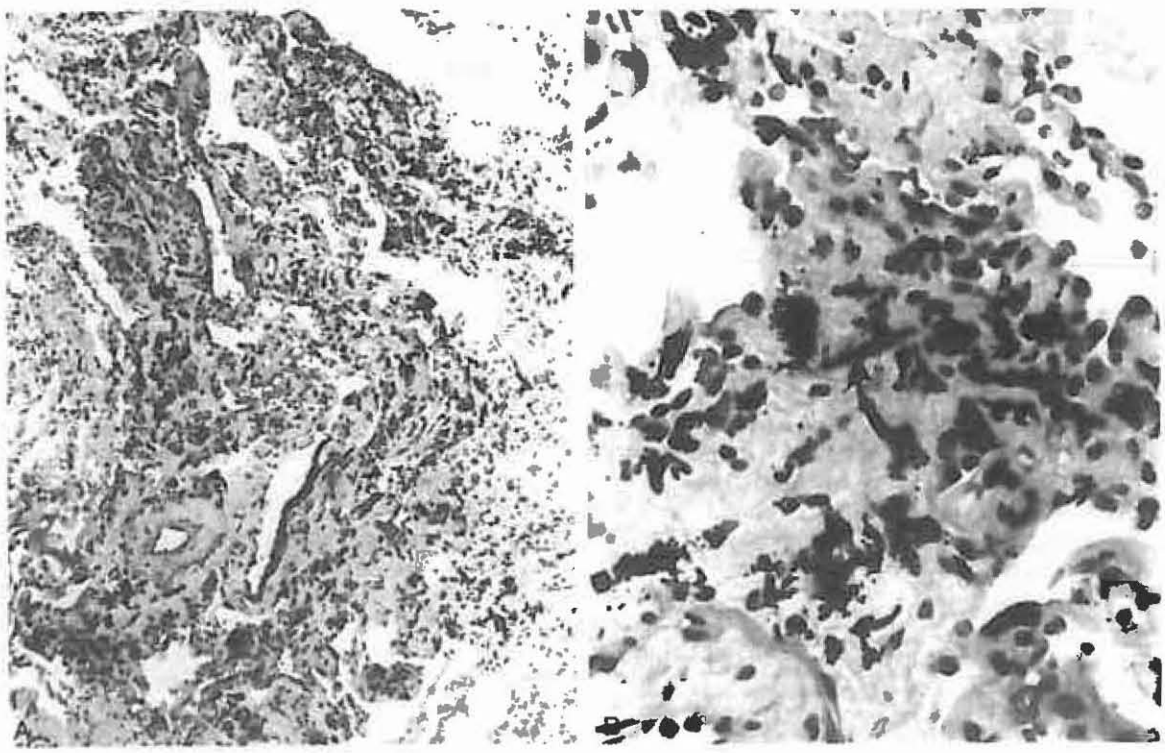

FIGURE 20 *A* and *B*, Example of grade 1 asbestosis. This region of lung tissue shows peribronchiolar fibrosis in association with ferruginous bodies consistent with asbestos bodies *(arrow)*. (A × 125; *B* × 500.) (Courtesy of Sam Hammar, MD.)

pleura. Diffuse pleural thickening also is a common sequela of benign asbestos-induced pleural effusions, but as with pleural plaques, its pathogenesis remains unknown. Diffuse pleural thickening and extensive pulmonary fibrosis are the classic features of advanced asbestosis.

CLINICAL EVALUATION

Patient History

Fundamental to consideration of any of the asbestos-related outcomes and their probability is the occupational and environmental history of asbestos exposure. Three aspects of the history are critical: onset, duration, and intensity of exposure. Onset is of importance because of the characteristic latencies between first exposure and disease manifestation. For interstitial fibrosis, latencies shorter than 20 years do occur (virtually never shorter than 15 years unless exposures are massive), but they are rare and should heighten suspicion of other diagnostic entities. Similarly, pleural plaques are generally not present before 20 years after exposure. Diffuse pleural thickening, if it follows a benign asbestos effusion, is the one nonmalignant outcome that may occur relatively early following exposure and is apparent sometimes as soon as several years from first exposure, although mean latencies are still close to 20 years.

The duration of exposure also is an important factor in determining whether or not abnormalities are attributable to asbestos exposure. A general rule that is helpful to the clinician is that it is unlikely that exposure durations shorter than 6 months, regardless of intensity, will result in interstitial fibrosis. If the intensity of the exposure has been high and the duration of the exposure only a few months, asbestosis remains a possibility but other causes of interstitial fibrosis should be more aggressively pursued. The same 6-month rule is applicable to the development of pleural thickening, although shorter periods of exposure have been associated with pleural effects.

The intensity of asbestos exposure is best determined by information about the job or trade, the industry in which it was performed, and the circumstances of asbestos use or exposure and protection from it. Asbestos insulators, those individuals who mixed and applied asbestos, are a useful reference point of high-intensity exposure. Until the mid-1970s in the United States, it was common for insulators to work routinely without respiratory protection and to work in dusty, often poorly or unventilated environments. A number of other workers, such as electricians, carpenters, plumbers, and pipefitters, worked side by side with insulators, and although on average their exposures were lower than the asbestos insulators, their exposures were often of moderate to high intensity. Occupations with lower intensity of asbestos exposure, but still sufficient if of appropriate latency and duration to cause any of the known sequelae, are multiple and include, for example, many construction workers in the United States. An occupational history occasionally reveals unexpectedly high-intensity asbestos exposures in unusual jobs, such as in mixing asbestos powder into paints. In taking the history, it is important to inquire about how asbestos was encountered, recognizing that respirable dust is of concern and that the perceived level of dust in the environment serves only as an index of exposure because respirable fibers are not visible. Intact asbestos impregnated in material is not of concern in contrast to activities that disrupt it and generate

airborne fibers. A partial list of occupations with common asbestos exposure is provided in Chapter 35.

The individual with isolated pleural plaques usually is asymptomatic unless other nonradiographically apparent sequelae are present or plaques are extensive. Although individuals with diffuse pleural thickening often do not have symptoms, they may report the presence of dyspnea or difficulty with full inspiration. We have observed that patients with pleural disease may report the presence of episodic pleuritic or nonpleuritic chest pain that has no other explainable cause. Asbestosis, as with many other causes of diffuse infiltrative lung disease, is characterized by the insidious onset of cough and exertional dyspnea. The cough initially is nonproductive, but as disease advances, it may become productive with time, even in individuals who have never smoked. Asbestos exposure, independent of other pathologic endpoints, also has been implicated as a cause of industrial bronchitis (see Chapter 11.3).

Physical Exmination

The findings on physical examination may be minimal or absent even in the setting of significant radiographic and functional abnormality. Although they are not specific to asbestos-related interstitial fibrosis, basilar rales (often end-inspiratory or pan-inspiratory) are common, occurring in up to 60% of individuals with radiographic asbestosis. Rales are dose dependent and can occur in the absence of radiographic change. Finger clubbing also has been associated with asbestosis, but this condition generally is associated with more advanced disease; when seen in patients with evidence of only mild interstitial fibrosis, suspicion should be raised about the possibility of cancer.

Radiographic Features

The plain chest roentgenograph remains the standard for radiographic evaluation of asbestos-related disease, although CT is increasingly defining pleural and parenchymal changes that may be undetectable or less well defined by standard techniques. It is known that many pleural plaques not evident on standard radiographs are found on postmortem examination, by thoracoscopy or thoracotomy, or on CT. On posteroanterior chest x-ray, pleural plaques have a variable appearance depending on their location in the chest, commonly having the density of pulmonary nodules at the lateral chest walls and less density more medial to the chest wall. Noncalcified pleural plaques are difficult to detect in the medial two thirds of the lungs because they are then parallel to the x-ray beam and too thin for definition; calcified plaques, however, are sufficiently radiopaque to be detectable in all portions of the chest (Fig. 21). Plaques occur most commonly on the middle part of the diaphragm, on the posterolateral chest wall between the 7th and 10th ribs, and on the lateral chest wall between the 6th and 9th ribs. Plaques are often bilateral and asymmetric in distribution, but unilateral pleural plaques are sufficiently common that they are indicative of past asbestos exposure in the absence of other, often radiographically apparent causes, such as rib fractures.

Diffuse pleural thickening is considered present radiographically if there is a thickness of pleura greater than 1 mm seen medial to the chest wall on posteroanterior chest radiography. Distinguishing discrete from diffuse pleural thickening is not always easy. Table 18 describes some characteristics helpful in making this determination. Apical pleural thickening up to 10 mm is a common variant of normal, and because apical thickening alone would be unlikely to be explained by past asbestos exposure, definitions of pleural thickening usually refer to the chest wall below the level of the fourth intercostal space. Diffuse thickening often involves the costophrenic angle (Fig. 22). Interlobar tissue thickening may be the sole manifestation of asbestos exposure, but it may also occur in association with other pleural abnormalities or interstitial fibrosis.

Parenchymal changes on posteroanterior chest radiographs generally are basilar in location; however, with more advanced disease, the middle and even upper lung fields may become involved. A predominance of upper lobe fibrosis has been described in a small number of cases, but this is an unusual presentation that suggests the need to evaluate other etiologic entities. When opacities are sufficiently dense and appropriately located, they may obscure the definition of

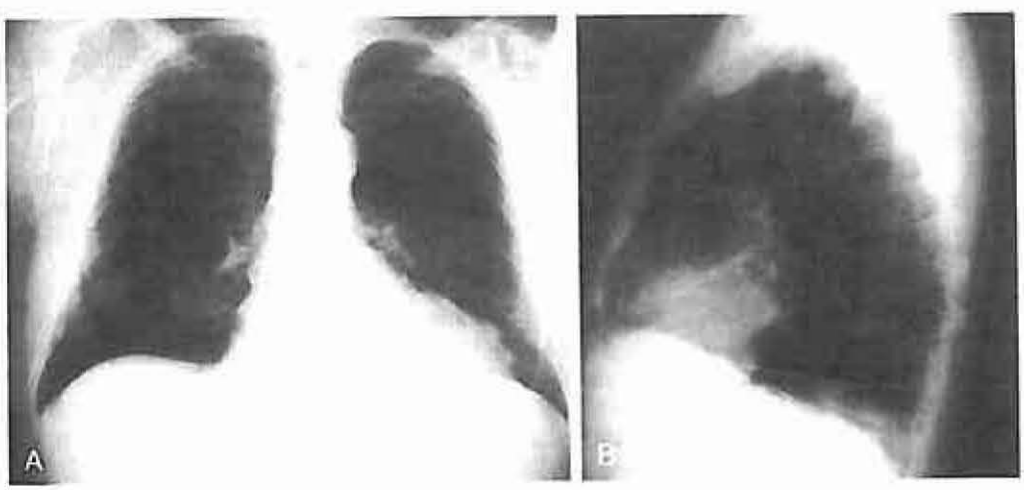

FIGURE 21 *A*, PA chest radiograph of 70-year-old retired insulator with calcified diaphragmatic pleural plaques and normal parenchyma (ILO 0/1). *B*, Lateral radiograph that better demonstrates calcified diaphragmatic plaques.

TABLE 18 Distinguishing Pleural Thickening from Extrapleural Shadows

	Pleural thickening		
	Discrete (plaques)	Diffuse	Extrapleural shadows
Composition	Parietal pleura	Parietal and visceral pleura (affects only visceral pleura if interlobar fissures)	Muscles (serratus anterior, external oblique), intercostal extrapleural fat, companion shadows
Location*	Lateral and posterior chest wall at level of lower ribs (5–10) sparing costophrenic sulcus; can involve mediastinum, pericardium, middle third of diaphragm	Usually bilateral, along lateral chest wall; may involve costophrenic sulcus	Companion shadows; most prominent in association with upper ribs Muscle shadows: apparent pleural shadows are in continuity with well-developed muscle shadows along lateral chest wall
Appearance on posteroanterior chest x-ray study	May be calcified	Rarely calcified	Not calcified
	Uneven, sometimes with bizarre shape, well-defined medial border when seen in profile (tangential to x-ray beam), faint when seen en face (parallel to x-ray beam). May show abrupt change in density from dense, lateral to faint, medial shadow	Ill-defined and irregular medial margin parallel to lateral chest wall; may show graded increase in density from medial to lateral border and widens inferiorly	Pleural line along lateral chest wall often widens superiorly and tapers inferiorly. Muscles have rhythmic, symmetrical appearance of triangular, V, or quadrilateral shape, with one sharply defined border, often fading into adjacent soft tissue
Appearance on right and left anterior oblique chest x-ray	Shadow remains adjacent to lung field with similar appearance to posteroanterior film except for rotation in orientation (and hence density) to x-ray beam	Shadow remains adjacent to lung field within thoracic cage; identify if greater than 10 mm width	Shadows demonstrated to continue with those of adjacent soft tissue and may rotate outside of lung fields. Fat: Rhythmic wavy appearance most prominent adjacent to rib rather than in intercostal space

*Apical pleural thickening alone (to level of 4th rib) is a variant of normal and should not be ascribed to asbestos unless associated with thickening below this level.

Adapted from Rosenstock L, Hudson LD. The pleural manifestations of asbestos exposure. Occup Med 1987; 2(2):383–407.

adjacent structures, causing the appearance of an irregular diaphragm or heart border, the latter known as the shaggy heart sign. There has been no convincing evidence that asbestos itself can cause progressive massive fibrosis or large opacities; although a few such cases have been reported in asbestos-exposed workers, it is likely that these manifestations are best explained by concomitant exposure to silica. The radiographic appearance of asbestos-induced interstitial fibrosis is characteristically small, irregular opacities, noted as s and t opacities by the ILO classification (see Introduction to Chapter 11). In advanced disease, opacities may have a honeycomb appearance (Fig. 23). Also of note, even among heavily exposed cohorts with a high prevalence of interstitial change, the large majority—often up to 90%—of abnormal chest radiographs fall in the mild grades of profusion by ILO criteria (1/0 and 1/1).

CT of the chest has become increasingly used in radiographic assessment of asbestos-related pleural and parenchymal disease. Conventional CT has been shown to be a more sensitive indicator than standard chest radiographs in detecting asbestosis. More recently, numerous studies have demonstrated the increased sensitivity of high-resolution CT to detect and characterize asbestos-related parenchymal change. Some characteristic features found in those with asbestosis include nondependent interstitial short lines (small nodules and single or branching lines less than 2 cm long and radiating from parenchyma to pleura), parenchymal bands (nontapering linear densities 2 to 5 cm in length that contact a pleural surface), and honeycombing. Correlations also have been shown between finding asbestosis on high-resolution CT and other evidence of asbestos exposure and effect, including ILO profusion scores, radiographic pleural thickening, and latency from sensitivity to first exposure. Specificity has been less well demonstrated for high-resolution CT in detecting asbestosis; nonetheless, it is reasonable to consider this technique as adding to the body of evidence that allows a high probability of accurate diagnosis in the setting of sufficient exposure of appropriate latency. At this time, however, given the additional economic and health costs of radiation exposure in using high-resolution CT, it is prudent to obtain high-resolution CT only in select instances, for example, when exposure and functional tests suggest the disease but the plain radiograph is not convincing.

Pulmonary Function

Pulmonary function tests are the most important tool for the functional assessment of nonmalignant asbestos effects. The isolated effects of asbestos-induced pleural disease are difficult to assess because nonradiographically apparent interstitial disease may be explaining or contributing to the findings. One study by Miller and associates (1983) of six asbestos-exposed workers with diffuse pleural thickening and normal parenchyma on posteroanterior chest radiograph showed a pattern characteristic of pleural-induced restriction and uninvolved parenchyma, namely, decreased vital capacity, decreased DLCO but an increase in the DLCO/TLC ratio, suggesting a relatively normal lung that has become encased.

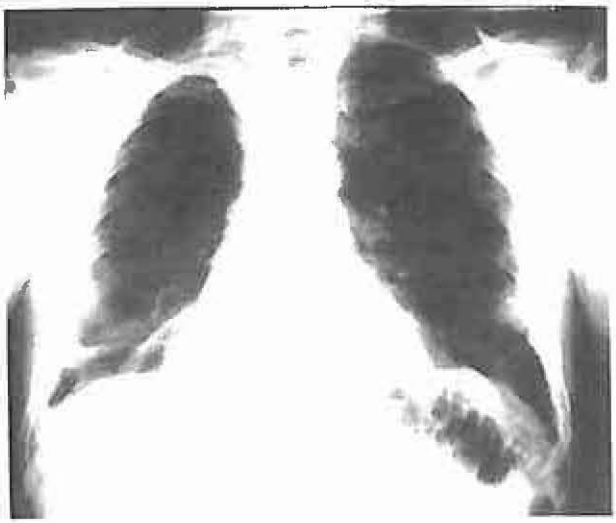

FIGURE 22 PA chest radiograph of 44-year-old asbestos insulator with diffuse bilateral pleural thickening and interstitial fibrosis (ILO 1/2).

These changes are in contrast to those typically found in asbestosis: decreased vital capacity and DLCO and a normal or decreased DLCO/TLC ratio.

It is now widely accepted that although pleural disease may have no functional consequences, it can in itself cause pulmonary function impairment. In rare cases, isolated pleural disease may be sufficient to cause respiratory failure and cor pulmonale. More common is the finding that isolated pleural disease can cause dyspnea and functional impairment in a restrictive pattern, and that these findings increase with any given grade of radiographic fibrosis. In those few studies that assessed the relative contribution to functional impairment of plaques versus diffuse pleural thickening, diffuse pleural thickening was found to confer a greater adverse effect.

The pattern of pulmonary function abnormalities in individuals with asbestos-induced parenchymal disease (asbestosis) is classically described as a restrictive one. Typical findings include decreased flow across all lung volumes, decreased TLC and residual volume, and abnormalities in gas exchange characterized by reduced diffusing capacity and widened alveolar-arterial oxygen gradient with or without hypoxemia. The earliest and most sensitive signs of asbestosis are decreased residual volume and diffusing capacity, which may occur in isolation or in combination. But isolated restrictive disease is but one presentation of asbestosis; mixed functional impairment also is common, which is explained in some but not all by concomitant cigarette smoking. There is ample evidence that asbestos itself can cause some degree of airflow obstruction, which is probably related to the fibrosis of terminal bronchioles; this effect has been demonstrated in nonsmoking asbestos-exposed workers and also in relation to the degree of asbestos exposure in workers after adjusting for effects of cigarette smoking. It is probably unlikely that isolated severe obstructive disease is attributable solely to asbestos exposure, but because of the competing forces on TLC in mixed impairment (restrictive disease causing a reduction and obstructive disease causing air trapping and an increase), it is not surprising that in individuals with asbestosis who have both obstructive and restrictive dysfunction, TLC is an insensitive measure of functional impairment.

Other Laboratory Tests

A number of other laboratory tests have been employed in assessing the pulmonary effects of asbestos exposure. Although BAL has been found to show increased numbers of neutrophils and asbestos bodies, the latter inconsistently correlated to dose, it is not a routine part of the diagnostic workup and is best reserved for excluding other etiologies. Similarly, gallium lung scanning, ultrasound testing, and other techniques have been used to assess parenchymal and pleural abnormalities; none deserves a role in routine evaluation of asbestos-exposed individuals.

Exercise lung function testing has been recommened by some investigators as a more precise means to assess the nature and extent of contribution of asbestos-related disease to impairment. When studied, there has been little correlation found between the extent of impairment as measured by static pulmonary function tests and lung impairment using maximal oxygen uptake (VO_2 max) and other parameters of exercise limitation. In summary, although exercise testing may uncover problems not evident in static pulmonary function tests and may help disentangle the contribution of ventilatory versus other causes of impairment, it has not proved useful as part of the routine evaluation of those with suspected or known asbestos-related nonmalignant conditions. It is probably best reserved for those individuals who have dyspnea that is out of proportion to radiographic and static lung function findings.

CLASSIFICATION OF NONMALIGNANT ASBESTOS-RELATED PLEURAL DISEASE

PLEURA
- Pleural Thickening
  - Plaques (Discrete Pleural Thickening)
  - Diffuse Pleural Thickening

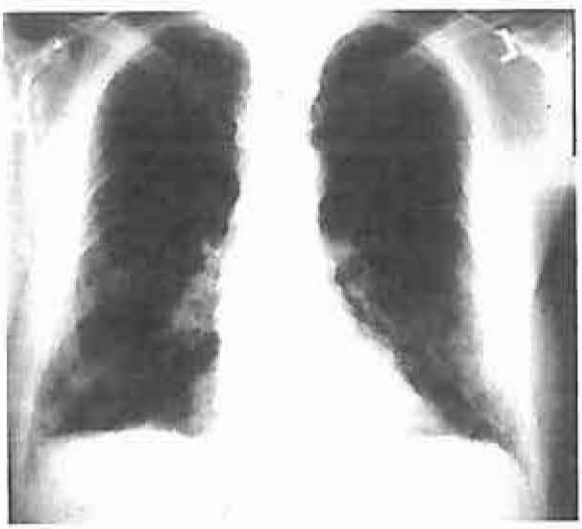

FIGURE 23 PA chest radiograph of 64-year-old painter with minimal diffuse bilateral pleural thickening and extensive fibrosis with honeycombing (ILO 3/3).

Benign Exudative Pleurisy
Rounded Atelectasis
PARENCHYMA
Asbestosis

Pleura

Pleural Thickening

Pleural thickening may be discrete (pleural plaques) or diffuse. These two abnormalities share many features in common but are worth considering separately because they may well arise from different mechanisms and appear to have a differential effect on symptoms and pulmonary function. The clinical importance of distinguishing between these two types of pleural abnormalities was not well established until recently, and the ILO classification of pneumoconioses did not code these separately until its most recent 1980 classification. There is good evidence that diffuse thickening is more likely than discrete thickening to cause functional impairment. A number of recently reported series of asbestos-exposed cohorts identify diffuse pleural disease as the predominant radiographic abnormality. Nevertheless, it is difficult to distinguish these entities radiographically, although criteria can be applied that show reasonably good correlation with CT findings. CT is more sensitive to the detection of pleural abnormalities and better able to separate diffuse from discrete changes than plain radiographs.

In addition to the potential for pleural disease to affect pulmonary function, several other aspects of pleural thickening are worth considering, such as (1) bilateral pleural thickening and even otherwise unexplained unilateral thickening are epidemiologic markers of past exposure; (2) pleural thickening, independent of exposure dose, may reflect an increased biologic responsiveness to asbestos; and (3) once present, pleural involvement is likely to become more extensive with time.

Pleural thickening when seen radiographically and without other obvious cause should always prompt a thorough occupational and environmental history to identify past asbestos exposure. It is helpful to the clinician that the differential diagnosis of discrete pleural thickening is limited (Table 19). Many of the causes other than asbestos of noncalcified plaques are likely to be unilateral, further limiting the likelihood that bilateral lesions are not due to asbestos. Both mica and talc have been identified as being able to induce lesions similar to those caused by asbestos, which is often explained by the contamination of these products by asbestiform minerals. One way to distinguish calcified asbestos plaques from those of other causes is that nonasbestos plaques are more often unilateral, more often extensive, and unlike those due to asbestos, often involve the visceral pleural, so that a thickness of pleura often may be seen between the calcification and the ribs. The differential diagnosis of diffuse pleural thickening is broader than for plaques, but it is often possible on the basis of other radiographic changes or clinical history to exclude other likely causes (Table 19).

TABLE 19 Differential Diagnosis of Pleural Thickening

Discrete	Diffuse
Asbestos-related*	Asbestos-related
Mesothelioma	Loculated effusions
Lymphoma	Infectious processes* (e.g., tuberculosis, paragonimiasis, bilateral empyema)
Myeloma	
Metastatic cancer	
Post-traumatic*	
Post-infectious*	Collagen vascular disease (e.g., scleroderma, SLE, rheumatoid arthritis)
Mica and talc*	
Scleroderma*	
Chronic mineral oil aspiration*	Sarcoidosis
	Uremia
	Drug reactions
	Chronic beryllium disease
	Silicosis
	Mica and talc

*May calcify.

The concern that those with pleural thickening may have increased sensitivity to asbestos is a difficult one to address methodologically, but it arises from the following evidence: (1) those with pleural plaques are more likely to develop asbestos-induced parenchymal fibrosis than similarly exposed workers without plaques, and (2) there is an increased risk of lung cancer among similarly exposed workers who develop pleural disease. However, no study to date has adequately addressed an alternate hypothesis, namely, that the observed differences in risk for those with pleural thickening are solely attributable to increased level of exposure. For the clinician, however, identifying pleural thickening should serve as an added factor for increased vigilance in an asbestos-exposed individual for risk of other sequelae. In addition, the identification of otherwise clinically unimportant thickening may play an added role in prompting greater attention by the physician and patient to the importance of prevention and specifically to smoking cessation. Of interest is the accumulating evidence that although cigarette smoking, at least among heavy smokers, may increase the level of interstitial fibrosis among those with asbestos exposure, there is no evidence that cigarette smoke enhances the risk for asbestos-related pleural thickening.

Benign Exudative Pleurisy

This asbestos-related outcome may be the sole manifestation of exposure. Benign exudative pleurisy (BEP), also known as benign asbestos effusion, is defined as follows: (1) history of asbestos exposure, (2) confirmation of effusion by x-ray study or thoracentesis, (3) no other disease to better explain the effusion, and (4) no development of malignancy within 3 years of diagnosis. As described earlier, there is some evidence of a dose-response relationship between asbestos and this disorder, although its exact prevalence and incidence are unknown. The diagnosis is complicated by the fact that these effusions usually are transient, although they often leave the residua of diffuse pleural thickening or obliteration of the costophrenic sulcus in their wake. There is no evidence to suspect that there is a progression from benign asbestos effusion to mesothelioma, but mesothelioma should be high on the list of differential diagnoses because it can present with minimal evidence of a solid lesion and an exudative effusion that is indistinguishable from a benign one. Fluid characteristics are variable; commonly, the fluid is a sterile exudate that may be serosanguinous. One of the more specific findings that limits the differential diagnosis is an increased number of eosinophils.

Benign exudative pleurisy often is asymptomatic, may be unilateral or bilateral, is usually small but may on occasion be up to several liters in volume. The reported mean latency from first exposure varies among series, ranging from 14 to 45 years. Importantly, BEP can be seen within the first 10 years of exposure and, given the longer minimum latencies for other nonmalignant processes, it is not surprising that in one series of an asbestos-exposed population, it was the most common asbestos-related abnormality within the first 20 years of exposure. Pulmonary function may be abnormal, either directly due to the effusion or to the common concomitant findings of asbestos-related pleural or parenchymal change or both; in one series of patients with benign exudative pleurisy, 25% had restrictive abnormalities and 50% had disturbed gas exchange.

Rounded Atelectasis

Rounded atelectasis, or pseudotumor, is thought to arise when pleural thickening of the visceral or parietal pleura, or both, compresses underlying parenchyma to form a radiographically appearing nodule or mass. This undoubtedly is the least common of the manifestations of exposure, although the exact prevalence is unknown. The radiographic appearance of these nodules is characteristically irregular and may have what has been termed the comet tail or broom sign, that is, pleura, bronchi, and blood vessels swirl from the hilum toward the rounded mass. Both bronchography and CT provide adequate anatomic definition of the pleural base of the lesion and its distinctive features. Nonetheless, in the asbestos-exposed individual with pleural thickening and suspect rounded atelectasis, the risk for bronchogenic carcinoma remains so high that prudent clinical judgment would treat all solitary nodules as suspect malignancies (Figs. 24 to 27).

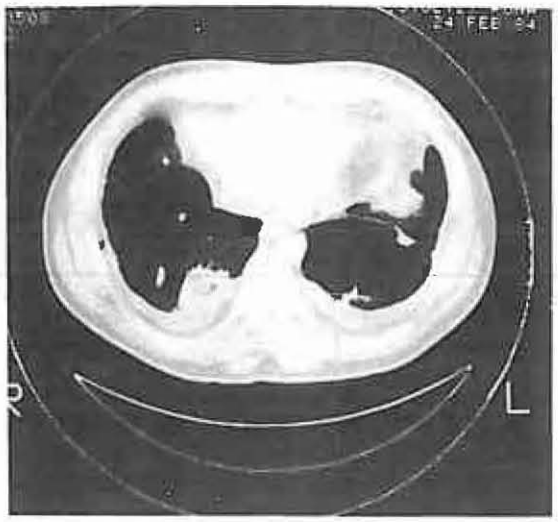

FIGURE 25 Chest CT of patient in Figure 24, showing right-sided posterior mass found at resection to be rounded atelectasis.

Parenchyma

Asbestosis

Although some investigators have used the term asbestosis to encompass nonmalignant asbestos-related pleural abnormalities, it is employed here to refer solely to the interstitial fibrosis and accompanying peribronchiolar fibrosis found in the parenchyma of affected individuals. As described earlier, this fibrosis may or may not be accompanied by pleural thickening and other pleural abnormalities.

The radiographic features of asbestosis, described in an earlier section, are essentially no different than that of many other causes of diffuse infiltrative lung disease, particularly idiopathic interstitial fibrosis. Concomitant pleural change, which is present in about half of those with asbestosis, increases the likelihood that the radiographic fibrosis is, in fact, asbestosis; the absence of pleural change, however, in the setting of asbestos exposure and typical findings of parenchymal fibrosis by no means excludes the diagnosis.

Asbestosis is classically described as a restrictive lung process, with decreased diffusing capacity and impaired gas

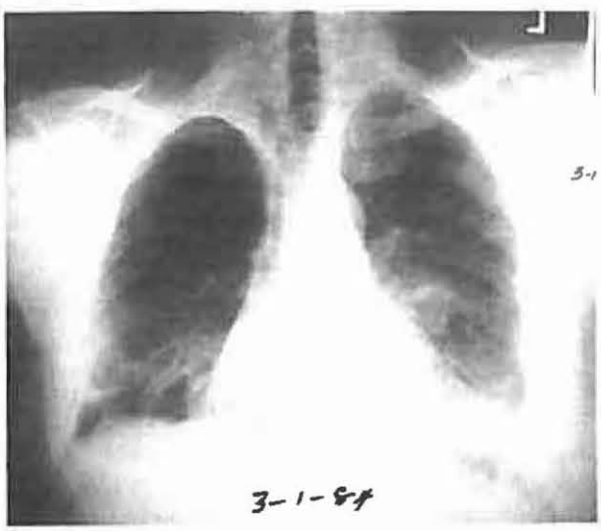

FIGURE 24 Posteroanterior chest x-ray of a 48-year-old insulator with a restrictive pulmonary impairment and exertional dyspnea, showing diffuse pleural thickening and bibasilar fibrosis (ILO 1/2).

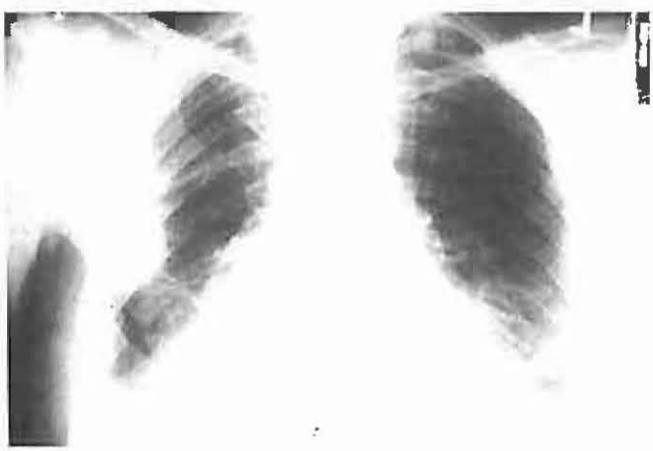

FIGURE 26 Posteroanterior chest x-ray of a 68-year-old brick mason with a restrictive pulmonary impairment and exertional dyspnea, and previous open thoractomy, demonstrating the right pleural-based mass as pleural fibrosis; bilateral diffuse pleural thickening and bibasilar fibrosis are present.

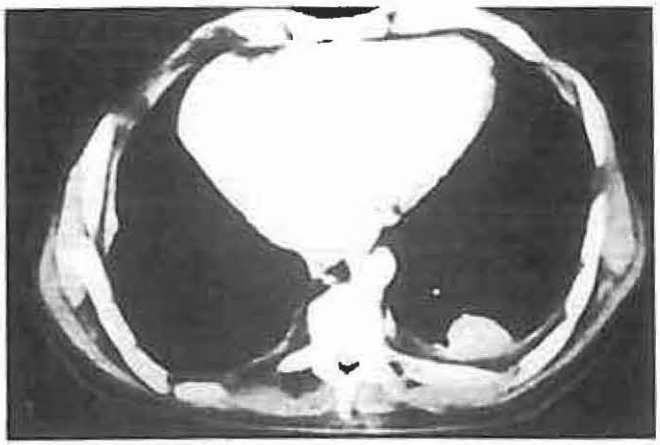

FIGURE 27 Chest CT of patient in Figure 26, showing left-sided posterior mass found at resection to be a well-differentiated adenocarcinoma.

exchange. Because many case series of those with asbestosis include an overwhelming majority of cigarette smokers, it has been stated by some that airway obstruction is an independent event not related to asbestosis. There are several lines of evidence, however, to suggest that asbestos exposure itself can cause airway obstruction. These include the pathologic findings of peribronchiolar fibrosis; the common findings of mixed obstructive-restrictive and isolated obstructive patterns in asbestos-exposed cohorts, which persist after controlling for cigarette smoking; and the increasing number of studies of nonsmoking asbestos-exposed workers that report airway dysfunction. The contribution of cigarette smoking—whether additive or synergistic—and the relative importance of parenchymal fibrosis versus dust load itself are undoubtedly important but not well defined factors in the risk for airflow obstruction.

The natural history of asbestosis is variable and not clearly explained by exposure parameters, such as intensity, duration, and effect of exposure cessation. There is good evidence that a significant proportion of those with asbestosis, even if exposure ceases, will worsen radiographically with time. Asbestosis is characterized by an accelerated loss of pulmonary function, although the loss may be episodic, perhaps related to intervening bouts of alveolitis. Studies about the role of cigarette smoking have been inconsistent, but a pattern emerges that at least among very heavy cigarette smokers who have been exposed to asbestos, there will be an increased risk for a higher grade of profusion abnormality (increased radiographic interstitial fibrosis) but not necessarily an increased prevalence of fibrosis.

DIAGNOSIS AND TREATMENT

Because many of the nonmalignant asbestos-related pulmonary changes do not occur in isolation, the following discussion provides a general overview of the approach to individual patients with asbestos exposure at risk for these sequelae. The importance of diagnosing benign exudative pleurisy and rounded atelectasis rests largely on the need to exclude other diagnoses, particularly asbestos-related malignancies. The finding of isolated pleural thickening in an asbestos-exposed individual usually can be attributed to asbestos exposure when other causes are excluded, which is almost always possible by other radiographic findings and a routine health examination.

Although CT examination is both more sensitive and specific than the chest radiograph in diagnosing asbestos-related pleural thickening, it is rarely needed. There is a greater likelihood that diffuse pleural thickening identified on plain radiograph will emerge on CT as extrathoracic fat in obese patients. However, because there is no specific medical intervention once a diagnosis of pleural thickening is made, excluding this possibility is not likely to be of any individual clinical benefit.

The diagnosis of asbestosis, as with pleural thickening, rests on a history of sufficient exposure of appropriate latency and clinical, radiographic, and pulmonary function findings. The exposure history is a necessary but insufficient criterion; a useful rule of thumb is at least 6 months of a moderate intensity of exposure no less than 20 years from first exposure. Clinical, radiographic, and pulmonary function features are variably present. The patient with the classic presentation has basilar rales, ILO profusion abnormalities 1/0 or greater (the minimal grade of interstitial fibrosis), and restrictive or mixed restrictive-obstructive impairment. A patient with asbestosis, however, may have the examination and pulmonary function findings just described, but he or she may also have an x-ray study showing only a modest increase in interstitial markings that do not clearly represent fibrosis (0/1 by ILO criteria). This should not be surprising, given the high percentage in some series (up to 15%) of histologic fibrosis in the setting of a normal chest radiograph. The sensitivity of chest CT increases the probability of finding interstitial fibrosis not otherwise radiographically apparent, but the use of CT should be selectively employed. Chest CT is probably best reserved for cases in which there is clinical concern about excluding other diagnostic entities. Lung biopsy provides the definitive diagnosis, but this invasive procedure has no role in routine diagnosis; it should be undertaken only when there is sufficient need to identify alternative, more treatable entities.

There is no evidence that removal of the affected person from further exposure will alter the natural history of asbestos-related pleural or parenchymal fibrosis. Nonetheless, given the dearth of effective secondary interventions, it is prudent to eliminate or otherwise keep all future exposures to a minimal level. Because of the economic implications of such intervention for individuals, particularly those who are minimally affected, these decisions should be assessed on a case-by-case basis. Factors to be considered in whether or not even minimal exposure should continue are the extent of disease and the intensity of exposure likely in the job. Individuals with asbestos-related pleural or parenchymal fibrosis, as with all asbestos-exposed workers, should be strongly encouraged and supported to stop smoking, given the profound synergism between asbestos and smoking and lung cancer risk.

Although there is no clear evidence of the benefit of ongoing medical surveillance once a diagnosis of pleural or parenchymal abnormalities is made, a Canadian task force on occupational respiratory diseases has made the following recommendations, which provide useful guidelines: (l) occupationally exposed asbestos workers with normal chest radiographs and spirometry should receive an x-ray examination

and spirometry every other year and (2) those with ILO category 1 profusion changes or suspicious symptoms or physical findings (e.g., increasing dyspnea or rales) should receive annual x-ray studies and spirometry and full pulmonary function tests on alternate years. Medical monitoring for those with isolated pleural thickening should probably be no less than that recommended for those with normal radiographs, namely, biannual spirometry and x-ray studies, with more frequent testing in the presence of increasing symptoms or extensive pleural involvement.

Steroids have no proven efficacy in the treatment of asbestosis, although no well-designed randomized trials have been performed to assess this question. It is possible that a subset of individuals with progressive disease related to ongoing or episodically active alveolitis would benefit from this intervention, either alone or in combination with cytotoxic agents. Accordingly, the use of steroids is not routinely recommended but may be considered on a case-by-case basis with close monitoring of objective parameters (e.g., DLCO) to guide continuation of therapy. Other interventions are prompted by symptoms and findings. Airflow obstruction should be treated like that of any cause. Infections should be promptly treated, although unlike silicosis, there is no evidence that asbestosis is associated with increased rates of tuberculosis or other atypical infections. Influenza and pneumococcal vaccines, even for younger affected individuals, are probably indicated.

Finally, the identification of these asbestos outcomes has the potential for affording affected individuals the benefit of workers' compensation, which varies in the United States on a state-by-state basis. In general, workers' compensation covers the costs of medical care, including medical monitoring and treatment of complications, vocational rehabilitation, if needed, and coverage of attendant impairment and disability.

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