Leslie Preger

SECTION 2
PULMONARY FIBROSIS

Inorganic dusts may be fibrogenic, such as asbestos and free silica, or non-fibrogenic, such as iron and tin. Diffuse pulmonary fibrosis represents an end-stage lung response to many other causes, much as ulceration is common to many colonic diseases and nephrosclerosis to many renal insults. Thus, other conditions must be borne in mind when assessing the radiographs of those with asbestos exposure, since not only are there similarities but also two conditions may coexist, e.g. sarcoidosis and asbestos-related pleural plaques or changes due to silica and asbestos as in cement-asbestosis, and in addition, asbestos workers may be free of asbestos-induced lung disease but have pulmonary changes resulting from some other disease or drug causing fibrosis.

A brief classification of the causes of widespread pulmonary fibrosis is given based on pathophysiological etiology[1] and contains three main groups:

1. Fibrosis secondary to granuloma formation
2. Fibrosis secondary to alveolar exudate
3. Fibrosis secondary to inorganic dust

FIBROSIS SECONDARY TO GRANULOMA FORMATION

In the acute stages of sarcoidosis, berylliosis, and extrinsic allergic alveolitis due to inhalation of organic dusts, granulomas are formed in all zones of the lungs. However, in the healing stages, fibrosis is predominantly in the upper zones.

FIBROSIS SECONDARY TO ALVEOLAR EXUDATE

Inflammatory and noninflammatory exudates may progress to diffuse alveolar wall fibrosis. Cytotoxic agents such as O_2, busulphan, hexamethonium, bleomycin, beryllium, and vanadium may be responsible. Exudates resulting from hypersensitivity to nitrofurantoin and salazopyrine may lead to fibrosis. Aspiration and viral pneumonias and the changes due to disseminated intravascular coagulation may lead to diffuse fibrosis. All of the above may have definable radiographic changes. The fibrosis that may follow continuous elevation of left atrial pressure rarely is demonstrable radiographically. A final group, where immunologic factors are possibly important, include acute cryptogenic fibrosing alveolitis, systemic lupus erythematosus, and idiopathic hemosiderosis. In this broad group of diseases, pulmonary fibrosis is a sequel of tissue necrosis and occurs predominantly in the lower lobes (the necrosis may persist, so that healing is by scarring and not by resolution).

FIBROSIS SECONDARY TO INORGANIC DUST

It has been noted that fibrosis secondary to granuloma occurs predominantly in the upper lobes, while that following alveolar exudates occurs mainly in the lower lobes.[1] The fibrosis that follows inhalation of silica and coal dust is usually found in the upper zones, but that related to asbestosis is usually more apparent in the lower zones. There has been no acceptable explanation for this difference. Since there is preferential ventilation of the lower lobes, the corollary that there is impaired clearance from the upper lobes could be used to explain the upper lobe predominance of silicosis. It is apparent that no single theory can explain satisfactorily the upper lobe fibrotic changes in silicosis and the lower lobe changes in asbestosis, especially when recent reports state there is a more or less uniform distribution of inhaled ferruginous bodies[2] and asbestos fibers[3] throughout the lungs. Earlier reports stated a more basal distribution of these bodies.

MICROSCOPIC APPEARANCE

The basic lesion of asbestos-related pulmonary fibrosis is widespread peribronchiolar fibrosis. This is the end stage. Initially there is an intraluminal reaction within the alveoli to entrapped asbestos dust. Within the alveolar lumina the asbestos fibers, macrophages, and desquamated cell debris become organized by strands of reticulin and later collagen. The type I lining cells of the alveolar walls become replaced by type II granular pneumocytes. Some of the alveoli become walled off.[4] Initially, only the alveoli arising from scattered individual respiratory bronchioles are affected. With increasing asbestos dust exposure or with the advent of immunologic factors, an interstitial reaction spreads to involve other adjacent respiratory bronchioles and then spreads

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from these peripherally to their alveoli. It is customary to describe the fibrosis as interstitial despite the alveolar wall involvement.

The development of fibrosis has been studied in rats exposed to asbestos dust of varying intensity and for varying periods.[5] Transposing data obtained from experimental animals to humans may be misleading in that, for rats, the order of increasing fibrogenesis is anthophyllite and Canadian crysotile, crocidolite and Rhodesian crysotile, and finally amosite, which does not parallel clinical experience. Of value, however, is the similarity of histological appearances in animals and humans. In both experimental animals and patients macrophages collect in the alveoli in which the fibers become deposited, and the alveolar walls react by replacing their type I lining cells by type II granular pneumocytes. This is reminiscent of the findings in desquamative interstitial pneumonia[6] in which type II granular pneumocytes line distal air sacs, and radiographs show a predominantly basilar change; desquamative interstitial pneumonia is probably an early stage in the development of diffuse fibrosis from many causes. As the experimental lesions progress, the reaction spreads to involve the adjacent respiratory bronchioles, alveolar ducts, atria, and alveoli, and coalescence of nearby involved areas occurs. Much of the lung parenchyma is eventually replaced by collagen, which distorts airways to leave air spaces that contribute to the honeycomb appearance seen on radiographs.

GROSS APPEARANCE

The lower lobe preponderance has been commented on. Involvement of the upper or middle lobes may be seen in severe cases or when the patient has been exposed to quartz, silicate or talc[7] in addition to asbestos. The fibrosis is usually plentiful in subpleural areas, giving the lung surface a whitish, puckered appearance up to 1 cm thick. The parenchyma when cut is brown-red and feels indurated. The lung volumes are reduced in severe cases; if there is much accompanying panlobar emphysema and only mild fibrosis, lung volume may be increased. Hilar node involvement does not occur unless there is a mixture of asbestos and silicosis. If bronchiole thickening and distortion are severe, the cut surface of the lung may exhibit a "honeycomb" appearance, the walls of the honeycomb "cells" being the interweaving fibrotic airway walls.

PATHOGENESIS

The laying down of collagen by fibroblast is termed fibrogenesis. In asbestosis, the fibrosis is diffuse, while in silicosis, it is more nodular. The pathogenesis of asbestos-related fibrosis may be considered under three aspects:

1. The role of macrophages
2. Influence of fiber size and shape
3. Immunologic factors

Role of Macrophages

The mechanism of fibrogenesis is probably the same for all asbestos fibers, even though amosite and crocidolite are more fibrogenic than chrysotile and anthophyllite. The wandering macrophages that are attracted to inhaled asbestos fibers play a key role. It is thought that the strongly fibrogenic fibers (amosite and crocidolite) stimulate macrophages to release substances that induce fibroblasts to lay down collagen and so produce fibrosis. The less fibrogenic fibers, chrysotile and anthophyllite, are more cytotoxic and may injure the macrophages to such an extent that these fibrogenic substances are not released[8] or are released in smaller amounts.

The degree of macrophage cytotoxicity of asbestos is related to magnesium content. Adherence of fibers to surface membranes of macrophages is in part dependent on the presence of magnesium hydroxide, the removal of magnesium, or its inactivation by chelation, which will reduce the surface cytotoxic effect of chrysotile.[9] Sialoglycoproteins in cell membranes interact with asbestos fibers to produce protein clusters that alter cell membrane permeability and may allow early release of fibrogenic substances from the macrophages. A defense mechanism is present in that the surface macrophage cytotoxic effect is inhibited by the presence of human protein or bronchial secretions.[10]

Following the attachment of asbestos fibers to macrophage surface membrane and initiation of the early cytotoxic effects described above, some of the fibers of small size are ingested and interact with membranes around secondary lysosomes. There is then a secondary release of enzymes, such as β glucoronidase, β galoctosidose and lactic dehydrogenase, lipids, and lipoproteins that cause adjacent fibroblasts to lay down collagen. Ferritin is synthesized in the secondary lysosomes containing asbestos fibers and contributes to asbestos body formation.[8]

Thus, asbestos probably does not have a direct effect on fibroblasts in producing pulmonary fibrosis. Instead, asbestos fibers are absorbed onto the surface of macrophages, the smaller particles ingested, and fibrogenic substances released in two phases as described above.

A purely mechanical effect of asbestosis fibers in the production of fibrosis is not generally accepted. However, evidence for a mechanical effect is quoted by Harrington.[11] There is, however, some conflicting evidence in regard to pleural fibrosis being produced by mechanical effect after inoculation of pleural space in experimental animals.[12]

The role of chemical factors, including trace elements associated with asbestos fibers in fibrogenesis, has been considered. Asbestos fibers are soluble to varying degrees, with chrysotile more soluble than the amphiboles (amosite, anthophyllite, and crocidolite), and silicic acid and metals in or on the surface of asbestos fibers are potential causes of fibrosis. The various biologically active metallic cations probably play a part via an effect on macrophages as indicated above.

Role of Fiber Size and Shape

Fiber size and shape govern penetration of and retention in airways, and particle size is a factor in ingestion of fibers fragmented by macrophages. The characteristic size and shape of asbestos fibers are shown in Figure 2-6; the amphiboles are rectilinear but of varying diameters, the largest being anthophyllite, then amosite, and finally crocidolite, while chrysotile is curly or serpentiform in shape. The diameter of chrysotile bundles varies with aggregation of fibers, but the fibers fragment, and ultimate chrysotile fibers may have a diameter as small as 0.03 μm.

Asbestos fibers larger than 200 μm are unlikely to penetrate nasal passages but may reach the lower airways in mouth breathers. Once past the nose, even long thin fibers may pass through the trachea and major airways and reach respiratory bronchioles where they tend to be deposited at bifurcation sites. In addition to length, fiber diameter is important, the aerodynamic diameter of the asbestos fibers and particles controlling their falling speed. Asbestos fibers of diameters greater than about 3 μm are unlikely to reach alveoli. Most of inhaled fibers do not reach the lower airways because the ciliary escalator mechanism is so efficient that 99 percent is removed from the airways, although some of this will be subsequently passed over the epiglottis and swallowed, with implications in induction of gastrointestinal malignancy.[13]

The needlelike amphiboles penetrate the lung more effectively than do curly chrysotile fibers, but since chrysotile has a tendency to physically disintegrate into fibers of short arcs, these fragments may behave as the rectilinear amphiboles.[14] Further penetration of fibers and particles to the pleura occurs via interstitial lymph and macrophages. Experimental studies show fibers in subvisceral pleural location in the following order of descending concentration: crocidolite, amosite, anthophyllite, and chrysotile.[15] Relating penetrability to fiber type requires qualification in that fiber size varies with the stage of processing, being greatest in mining and least, and therefore of more penetrating power, in the asbestos textile industry. Size and shape may vary within mineralogic type, Australian crocidolite being of a smaller diameter than South African N.W. Cape crocidolite, which is, in turn, of finer diameter than Transvaal crocidolite.

Fiber particle size limits ingestion by macrophages. Short fibers (less than 5 μm) are completely ingested by macrophages, intermediate size particles (5–25 μm) may or may not be completely ingested, and long fibers (more than 25 μm) are never completely taken up. With the long fibers, several macrophages may be needed to completely engulf a single fiber.[8] Longer fibers are more fibrogenic than short ones. Long ones are less well phagocytosed and transported away.[11] Lauweryns and Baert provide a recent excellent and detailed account of alveolar clearance of particles and the role of the pulmonary lymphatics.[16]

Immunologic Factors

There is experimental work suggesting that antinuclear antibodies may accelerate disease started by a different agent, and antinuclear antibodies are found in 25 percent of asbestos patients,[1] those with severe fibrosis usually being ANA positive. Initial reports suggested that the presence of HLA-B27 antigens makes an asbestos worker more susceptible to the development of severe as opposed to mild pulmonary fibrosis. More recently, this has been disputed. In a group mainly exposed to chrysotile, there was no correlation between HLA-B27 antigen prevalence and the presence or absence of pulmonary fibrosis.[20] But HLA-B12 was more prevalent in those with pulmonary fibrosis and HLA-BW5 was more prevalent in those without pulmonary fibrosis, raising the possibility that these two antigens provide susceptibility to or protection from the development of fibrosis. The matter is discussed more fully in Chapter 1.

Relation Between Asbestos Dust Burden and Severity of Fibrosis

The retained asbestos load in the lung may be estimated by many techniques. If light microscopy is used, only fibers of 0.4 μm or greater in diameter will be seen; since most asbestos dust particles are less than 0.3 μm diameter, electron microscopy is needed for an accurate estimate. Fortunately, the percentage of optically visible fibers is reasonably constant between 12 and 30 percent of total, so that light microscopy data may be extrapolated to give an estimate of total asbestos load.[17].

Using these techniques, the dust load–fibrosis relationship for asbestos differs from that found with silicosis. In the latter the severity of pulmonary fibrosis is proportional to the silicic content of the lungs. With mild and moderate asbestos loads in the lungs, there is an increasing severity of pulmonary fibrosis, but in severe pulmonary fibrosis, there is no correlation with a further increase in fiber concentration.[18] Additionally, no relationship was

found between severity of pulmonary fibrosis, duration of exposure, time from first exposure, or time from last exposure to death. The suggestion is made, at least for the amphiboles that were the predominant fiber, that mild and moderate degrees of pulmonary fibrosis are proportionately related to dust burden but that further transition to severe pulmonary fibrosis depends on the interaction of some additional factors. Infection is one possible factor,[19] and prompt treatment would thus be needed even in apparently minor respiratory infections in asbestos workers to halt progression of fibrosis. A second possibility is that the asbestos fibers may initiate fibrosis that may progress to a moderate severity but that an immune mechanism may intervene to produce severe fibrosis.

VARIANTS OF ASBESTOSIS

Asbestos-related pulmonary fibrosis may be atypical, and there are some variants of clinical and radiological interest:

1. Cryptogenic fibrosing alveolitis
2. Household contact asbestosis
3. Massive fibrosis
4. Caplan's syndrome
5. Cement asbestosis

Cryptogenic Fibrosing Alveolitis

A proportion of patients thought to have nonspecific interstitial pulmonary fibrosis (cryptogenic fibrosing alveolitis) may have an undetected history of asbestos exposure or a biopsy specimen may have been examined with light microscopy only and a false underestimate of asbestos burden obtained. This may apply especially to chrysotile, which fragments into tiny particles. In one patient, light microscopy revealed fibrosis and inflammatory changes but no ferruginous bodies.[21] Electron microscopy showed large numbers of small (less than 5 μm) chrysotile fibers. The inference was made that some patients diagnosed as having fibrosing alveolitis or desquamative interstitial pneumonia may, in fact, have asbestosis.

This inference produced some engagingly sarcastic correspondence in the *New England Journal of Medicine* with Miller et al.[22] restating their belief that particles of less than 5 μm are fibrogenic, while Gross et al.[23] found this statement questionable.

Household Contact Asbestosis

Within the group of cryptogenic alveolitis patients, there are some who had household contacts with former asbestos workers who carried asbestos in their clothes, shoes, or hair. Anderson et al., in a study of 326 individuals who have had household contact with amosite asbestos workers, found 36 percent with pleural or parenchymal changes typical of asbestos exposure; children had a greater proportion of involvement than wives or siblings.[24] Pleural changes without pulmonary fibrosis were seen more frequently than pulmonary fibrosis alone. There were 4 patients in this group with pleural mesothelioma.

Massive Fibrosis

A third group includes those with massive upper lobe fibrosis.[7] The reason is unknown, but two-thirds of this group had positive PPD skin tests even though there was no clinical evidence for active tuberculosis. If one accepts the relationship between immunologic status and severity of pulmonary fibrosis in severely asbestotic patients, an analogy may be the upper lobe fibrosis seen in ankylosing spondylitis in which there is a strong association with HLA-B27 antigen. Discrete areas of massive fibrosis extending over areas of more than 1 cm may occasionally be seen in both upper and lower lobes. These have been reported in miners, and it may be that the high quartz content (6 percent of South African asbestos) is responsible.[25]

Caplan's Syndrome

An unusual group comprised those with asbestos-related pulmonary fibrosis who have or develop rheumatoid arthritis. Multiple rounded nodules appear on the chest radiographs, sometimes in crops and mainly in the lower lobes, but any area may be involved. Occasionally, the nodules are unilateral. The nodules vary in size from a few millimeters to a few centimeters; some may cavitate and, if so, may have thick or thin walls. The cavities may fill in later.

They are necrobiotic nodules, similar to those seen in the lungs of some patients with rheumatoid arthritis, but they differ in that they contain asbestos fibers and ferruginous bodies and are not accompanied by subcutaneous nodules. The nodules may proceed, accompany, or follow the onset of rheumatoid arthritis.

In deference to Anthony Caplan, who first described the nodules accompanying coal workers' pneumoconiosis,[26] this entity has been termed Caplan's syndrome in asbestosis.[27–30] This syndrome has also been noted in those

those exposed to silica and pottery manufacture, sand blasting, and brass and iron foundries.[3]

Cement Asbestosis

A large group of patients includes those with cement-asbestos pneumoconiosis. About two-thirds of world production of asbestos is used in cement production. The fiber type will vary with need: crocidolite is preferred when tensile strength and resistance to acid is important, and chrysotile is used if flexibility is needed. The asbestos is mixed in the proportion of 15 to 20 percent with artificial Portland cement that consists of calcium silicate, tricalcium aluminate, and tricalcium ferrite. Portland cement also contains 1 to 3 percent free silicate (SiO_2) and smaller amounts of other oxides (Al, Fe, Mg). Exposed workers may develop a combined pneumoconiosis due to asbestos and silica. Asbestos produces mainly lower lobe fibrosis with irregular and linear opacities, while silica causes rounded parenchymal densities, progressive massive fibrosis, and hilar enlargement with egg shell type calcification.

CLINICAL FEATURES

The symptoms of pulmonary fibrosis may be summarized as dyspnea frequently with dry cough, and occasionally chest pain. Physical signs may include restricted chest movement, end inspiratory crepitations, and digital clubbing. A broader account is given in Chapter 1.

RADIOGRAPHIC CHANGES

General

Parenchymal radiographic changes resulting from asbestos exposure are not specific (see Figs. 2-29 and 2-30). Excluding the characteristic pleural plaques, the parenchymal changes are those of interstitial fibrosis, which is more severe in the lower lobes, and this finding is common to many disease entities, e.g., scleroderma, desquamative interstitial pneumonia, recurrent aspiration pneumonia, and bronchiectasis. It is therefore important to examine radiographs showing pulmonary fibrosis for the presence of calcified asbestos plaques, since these may act as biological markers to suggest the



Fig. 2-29. *(A and B) The more typical basilar distribution of pulmonary fibrosis due to asbestosis is demonstrated (arrow). There is coincidental upper lobe paraseptal emphysema. (B* *on to the page)*

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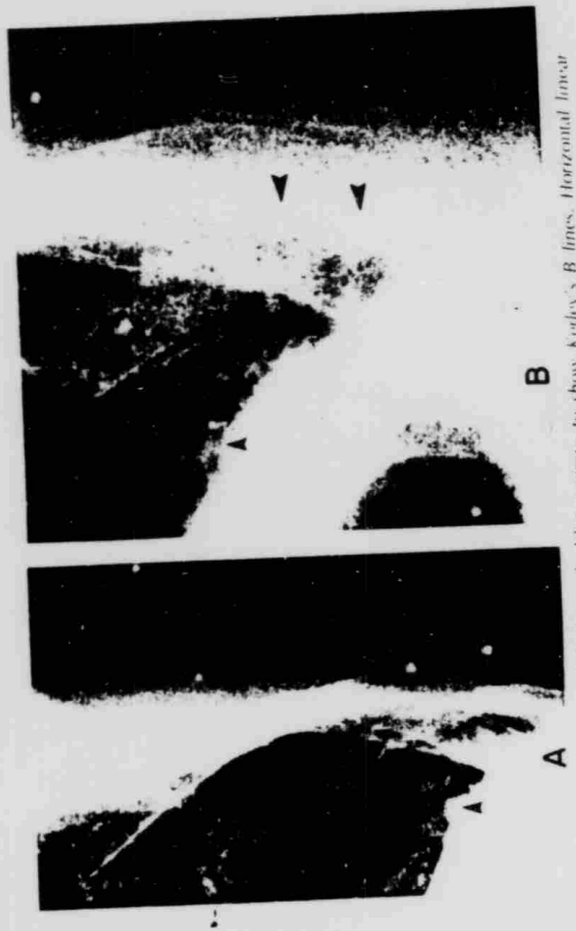


Fig. 2-30. *(A and B) PA and oblique views to show Kerley's B lines. Horizontal linear shadows (horizontal arrows in B) as a result of thickening of interlobular septa is common in shadows (horizontal arrows in B) as a result of thickening of interlobular septa is common in asbestosis. The interlobular septa may be weakened into broad fibrous bands, frequently wider than usual, seen with B lines of carcinogenic or oncogenic origin. The interlobular septa may be more apparent in oblique view (B) (see facing page). There are subaxillary and diaphragmatic plaques (vertical arrows). The incidence of plaques in pulmonary fibrosis has been underestimated with conventional techniques. CT shows many plaques not seen [illegible]*



Fig. 2-31. *Lower lobe fibrosis and bullae adjacent to diaphragm (arrows). Contraction of fibrous areas frequently leads to bullae development. A subaxillary plaque is present (oblique arrow).*

cause of the fibrosis (see Fig. 2-31). A proportion of patients with asbestos-related pulmonary fibrosis do not show plaques. In Solomon's series 25 percent of the South African miners with pulmonary fibrosis did not have pleural plaques in chest x-rays.[32] A similar percentage is stated by Soutar et al. in a study of 84 patients with industrial (nonmining) exposure to asbestos.[33] The absence of plaques has been attributed to differing etiologic mechanisms in the development of plaques and fibrosis or the entrapment of fibers in fibrotic areas so that the pleura is not reached. The latter seems improbable, since the number of plaques increases with the severity of the fibrosis.[34]

The parenchymal fibrotic changes may be classified according to the ILO U/C classification (see Chapter 3) into opacities that may be small or large, rounded due to silica or irregular due to asbestos. Both rounded and irregular opacities coexist if there has been exposure to both of these substances, such as in asbestos cement workers. Rounded and irregular opacities may be present in those who have had asbestos exposure only. There is evidence (discussed later in this section) showing that true summation of overlying shadows will produce a more rounded density of the p, q, r type, while imperfect superimposition tends to produce an s, t, and u type pattern. Profusion of densities is thus of

more significance than is the type of density when ILO Classification is used for epidemiological or compensation purposes. The notation is thus purely descriptive and noninterpretative. This has value in epidemiologic surveys and compensation work. It avoids the dangers met with in clinical radiology, where descriptive terms have acquired an interpretative significance. Thus, "honeycombing" (Fig. 2-32) was first used to describe the late phase of histiocytosis X but is currently commonly applied to the pattern resulting from a variety of interstitial changes, whether from fibrosis as in pulmonary fibrosis, hamartomatous change as in tuberous sclerosis, or inflammation as in bronchiectasis.

In routine radiological assessment of pulmonary fibrosis, one may refer to the use of descriptive terms such as round or irregular opacities, but search should also be made for septal lines, ring shadows (honeycombing), and long hair line shadows.

Most septal lines seen radiographically are of two types, A and B (see Fig. 2-33). B lines are usually 1–2 cm long and are seen in the lower lung zones touching the pleura at the outer ends. A lines are less easily identified in pulmonary fibrosis because although they are longer than the B lines (2–4 cm), their position radiating from the hilus toward the pleura is often obscured by the fibrotic changes. A lines are therefore best seen in asbestosis in the upper zones, where pulmonary fibrosis is less severe. The B lines are best seen in the anterior and lateral parts of the lower zones in both frontal and oblique x-rays because in the lingula and middle lobe the connective tissue septa are well developed and the lobules are arranged vertically, resulting in short horizontal septa. The septal lines become thickened, and when extreme, part of the thickness is due to merging with alveolar interstitium that has fibrosed. The thickening extends to the visceral pleura. Retraction of these thickened septa may result in localized areas of panlobular emphysema. Thickened septal C lines producing a reticular pattern result from the visualization of connective tissue septa between peripheral lobules seen en face and superimposed on deeper septa randomly distributed in deeper parts of lung.[35] Confident radiographic identification is greatest with the B lines, less for the A lines, and least for the C lines. B-line identification is complicated by the similar appearance of fine fibrotic lines that occur in early pulmonary fibrosis as a result of thickening of the alveolar interstitium. When they extend to the pleura, differentiation from B lines is impossible. In Solomon's series,[32] 5 of 32 patients had such fine fibrotic lines, which Solomon characterized as fine fibrosis not due to Kerley B lines, while in Soutar's series,[33] 36 percent had septal lines.

Long hairline shadows on radiographs in areas of otherwise normal-appearing lung are an occasional finding; if they do not result from an accessory fissure or linear alveolar atelectasis, they may be due to a prior granulomatous or nongranulomatous inflammatory focus that has healed and

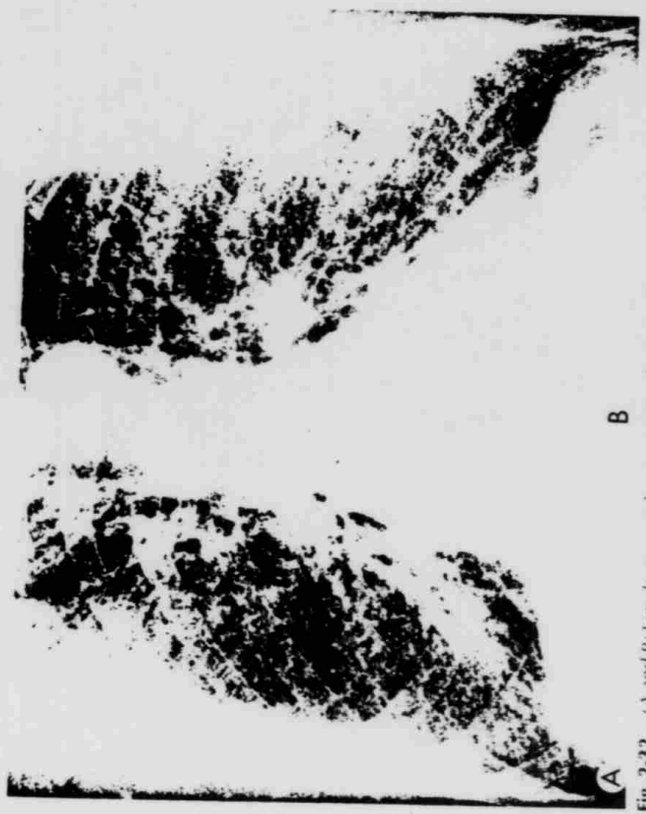


Fig. 2-32. *(A and B) Fine honeycomb appearance due to pulmonary fibrosis. This patient had hypertrophic pulmonary osteoarthropathy. Involvement of the upper lobes is greater than usual in asbestos exposure. Patient had a long exposure as a boiler constructor.*

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Fig. 2-33. *Pulmonary fibrosis in an asbestos worker. There are thickened interlob[ular] septa (some are indicated by arrows). The increased translucency due to a bulla at [the] left base allows better visualization of multiple irregularly shaped opacities typical [of] asbestos exposure. Note the ill-defined cardiac border due to adjacent fibrosis [and] mediastinal pleural thickening.*

disappeared. The length of these lines may be out of proportion to the prec[eding] focus.

Honeycombing is a radiographic finding in interstitial lung disease, [the] term being borrowed from the gross pathological finding. Since examination [of] x-ray films for most twentieth-century physicians has replaced the autop[sy] room organ recital of prior years, it seems a good term to retain. It indica[tes] replacement of normal lung by small cystlike spaces amidst extensive pulm[onary] fibrosis.[36] The spaces result from confluence of distal air spaces, and th[ey] are lined by atypical cells that have spread distally from the more proxim[al] airways.[37] The pattern is easily assessed with the naked eye on cut surfaces [of] fibrotic lung. On a chest radiograph the appearance is recognizable with[out] too much difficulty, but the radiolucent spaces among the fibrotic areas m[ay] represent not only the confluent air spaces lined by atypical epithelium but [also] areas of normal and uninvolved lung and foci of panlobular emphysema. It [has]

been suggested that the diagnosis of honeycombing should be made only [when] the radiolucencies are round or oval and when the margins are traceab[le] about 360 degrees.[35] This system is analogous to that used in the diagno[sis] other lung cavities. By convention, these radiographic spaces are not g[reater] than 4–10 mm wide and the thickness of their walls vary from hairline [to] mm.[38] Honeycombing was found in 36 percent of the Brompton Hospital [series] of industrial asbestos users.[38]

Honeycombing is one type of ring shadow. A second type seen in pu[l]nary fibrosis results from thickening of connective tissue around the proximal airways. If seen end on, the airway will present a ring shadow. [If] seen along its length, the airway will exhibit a more linear shadow. Becau[se] distortion, the linear appearance is generally more difficult to see in asbe[stos] related pulmonary fibrosis, although it is a classical sign of fibrosis assoc[iated] with bronchiectasis. The ring shadow may be of hairline thickness or wi[der] the fibrotic process has extended deeper into the previously aerated air[way]. The central lucency is due to intraluminal gas.

A shaggy outline of the cardiac silhouette is a nonspecific sign. It has [been] described in mediastinitis, chronic adhesive pericarditis, and pertussis. It [can] be due to disease of the pericardium, mediastinal pleura, or lung parench[yma] adjacent to the heart. In asbestosis, it may be due to thickening by plaqu[es] the mediastinal parietal pleural residua of benign pleural effusion affectin[g] mediastinal visceral pleura, or interstitial fibrosis in those parts of lingula [or] middle lobe adjacent to the heart. It was seen in 8 percent of William's ser[ies].

Small opacities, usually irregular and occasionally rounded in shape [with] margins that may be sharply or poorly defined, are seen as a result of asbe[stos] exposure. They become obscured if a severe degree of fibrosis develops. T[heir] size varies from a pinpoint to up to 4 mm in diameter for irregular opac[ities]. Large opacities are rarely seen except in variants such as cement asbestosis [or] as part of Caplan's syndrome with asbestosis. Based on histological studi[es] these small irregular opacities may originate in terminal air spaces in e[arly] stages or in peribronchial interstitium in more advanced phases. The for[ms] which are air space shadows, may spread by extension through airways [and] pores of Kohn, coalesce, and be characterized by indistinct margins. The la[ter] being interstitial in location, are surrounded by aerated air spaces and theor[etically] should have distinct margins. From a practical point of view, this distinc[tion] tion cannot be made on radiographs, since the densities seen, even tho[ugh] some may be rounded and some may be irregularly marginated are compo[site] shadows resulting from summation of overlying densities.[41] Superimpositio[n] opacities not in direct contact will result in poor marginal definition,[35] wh[ile] perfect superimposition will produce shadows of greater density that [are]

Table 2-4
Parenchymal Changes in Asbestosis

Findings	Frequency
Pinpoint	29% (many 15%, few 14%)
Irregular opacities 2–4 mm diameter	75% (many 29%, few 46%)
More than 4 mm diameter	20%
Diffuse haze (ground glass appearance, not obviously due to pleural changes)	13%
Septal lines	36%
Honeycombing	36%

[a]The designation "few" is equivalent to the ILO classification of profusion 1/1 and more profusion or 2/2 or more (see Chapter 1).

falsely suggest sharper margins. With widespread imperfect superimposition, a diffuse gray haze, sometimes referred to as having a "ground glass" appearance, will ensue.

In the group of 84 industrial asbestos workers seen by Soutar et al., the incidence of the above changes is given in Table 2-4.

Suboptimal radiography may result in an erroneous diagnosis of interstitial fibrosis. A radiograph that is underexposed may produce too dense a shadow of the pectoral muscles, simulating fibrosis. In such an instance the normal lung interior to the muscle mass will have a greater transradiancy while asbestos-related fibrosis in this area would show reduced translucency. A radiograph exposed during an incomplete inspiration, especially in a heavy patient, will show reduced translucency in the basal areas. The use of too low a kilovoltage may make identification of fibrosis difficult. In general there is a tendency to diagnose fibrosis too frequently when interpreting films of those known to have had exposure to asbestos. In particular, the presence of large confluent plaques seen en face produces a hazy appearance that may simulate fibrosis and is especially in this situation that high kilovoltage techniques are helpful.[a]

VARIANTS OF X-RAY APPEARANCE

Massive Fibrosis

Massive upper lobe fibrosis is usually symmetrical, but one side may be more involved, producing a tracheal shift. The upper lobes are diffusely involved with hilar retraction, tissular elevation, and rib crowding. Large

[a]Felson, B. Radiology of the pneumoconioses. A symposium sponsored by American College of Radiology, Jan 13–15, 1978, Washington DC. (unpublished)

fibrotic masses are occasionally present in the lower lobes, either alone or in combination with upper lobe fibrosis. The role of prior tuberculous infection or the quartz content of asbestos has been noted. The appearance has, however, been seen in some U.S. asbestos workers where quartz content is not a factor.

Caplan's Syndrome

The multiple nodular densities may be unilateral or bilateral, they can vary in size from a few millimeters to a few centimeters, they can necrose to produce thick or thin wall cavities, and they are occasionally accompanied by pleural effusion. The radiological differential diagnosis includes metastatic disease, Hodgkin's disease, septic infarcts, infectious granulomatous disease, Wegener's granulomatosis, staphylococcal pneumatoceles, fungal infections, especially in those with altered immunity, and rheumatoid nodules unrelated to any pneumoconiosis.

Cement Asbestosis

Silico-asbestosis is seen in cement workers who are exposed while mixing asbestos fibers with synthetic Portland cement, which contains calcium silicate. The mixture is then ground, which entails exposure to silica. Those workers exposed develop a mixed pneumoconiosis. Asbestos inhalation is responsible for the characteristic mid and lower zone fibrosis described earlier. Silicosis is responsible for occasional densities of progressive massive fibrosis (Fig. 2-34). In addition, there may be enlarged hilar nodes with eggshell calcification. The large fibrotic areas migrate medially, unlike the very rare localized areas of pulmonary fibrosis in pure asbestosis, which remain in unchanged location, usually in upper lobe. In addition, numerous small opacities are present. These are rounded or irregular in shape. The rounded shadows are due to the effect of silica and the irregular ones, to asbestos. A comparison of the opacities seen in asbestos workers[42] is outlined in Table 2-5. These data differ somewhat from the Bromptom analysis,[33] which although agreeing that irregular opacities are characteristic of asbestos, did include some tiny rounded densities (2-9 percent of those examined), but the radiographic findings were not related to the type of asbestos exposure. The profusion of rounded opacities correlates better with total mixed dust exposure than does the profusion of irregular opacities.[43] The fact that asbestos exposure alone, as opposed to mixed dust, produces mainly irregular small opacities is further suggested by data from workers in a Finnish anthophyllite mine.[44] Forty percent had small



Fig. 2-34. Cement asbestosis. The cement component of cement asbestosis is responsible for the large fibrotic mass in the upper lung fields and the smoothly rounded opacities which are more randomly distributed. Both lung attributed to the calcareous and free silica present in cement. The large fibrotic mass in the upper zones outlined with arrows. If the front view is examined with a hand lens, multiple round opacities will be seen; a prominent one is identified by an arrow in the frontal view. Lateral view shows diaphragmatic calcification secondary to asbestos.

Table 2-5
Cement Asbestosis

Opacity Type	Exposure to Cement Only	Exposure to Cement Asbestos	Exposure to Asbestos Only
Irregular	13%	60%	5%
Rounded	18%	10%	0–2% (some had rounded shadows alone, 2% had it
Pleural plaques			
Noncalcified	2%	2%	1%
Calcified	2	5%	0%

parenchymal opacities that were classified as irregular small opacities (36 percent), rounded small opacities (7 percent), and both types (7 percent).

The type of asbestos end product is of importance. Asbestos cement used for production of shingles contains chrysotile but no crocidolite, and those engaged in their manufacture have an immense excess burden of pulmonary fibrosis, while workers manufacturing asbestos cement pipe, which currently contains 3 percent crocidolite and higher percentages in the past, have a 5 to 6 percent burden of lung cancer.

RELATION BETWEEN RADIOGRAPHIC APPEARANCE, EXPOSURE DOSE, AND PULMONARY FIBROSIS

In cement asbestos workers with mainly mild to moderately severe pulmonary fibrosis, the profusion of irregular and rounded opacities is related to total dust exposure.[25] Lung volumes and maximal exploratory flow rates decreased in relation to increasing cumulative asbestos dust exposure. Pulmonary diffusing capacity was not related. Crocidolite exposure produced lower expiratory flow rates and reduced diffusion capacity when compared with chrysotile exposure.[45] Weill et al. concluded for their patients, who generally did not exhibit severe radiographic changes, that both radiological monitoring and pulmonary function testing were necessary to detect the earliest abnormalities in the largest number of exposed workers, since in individual patients, abnormalities may first be identified by radiograph, with pulmonary function tests being normal or vice versa.

More recently, Roberts et al.[46] in reviewing a large number of patients with pulmonary fibrosis but without an asbestos occupation exposure, thought that a rough estimation of the disease activity may be obtained from the radiographs in the early phases when changes in the alveolar walls and lumen are predominant. This produces a hazy pattern. Since the distribution is focal and scattered, an air bronchogram appearance is not seen, as opposed to the air bronchogram effect that may be seen in the early stages of more diffusely spread air space diseases, e.g., lobar pneumonia. In the intermediate stages, disease severity is more accurately assessed by physiological tests. It is at this phase that the smaller irregular densities of asbestosis become apparent. Radiographs again become of value in the later stages of the disease for detecting honeycombing due to severe fibrosis.

RADIOGRAPHIC DETECTION OF CANCER IN FIBROTIC LUNGS

A primary carcinoma is difficult to detect in a fibrotic lung (see Fig. 2-3
All types—adenocarcinoma, alveolar cell carcinoma, oat cell and squamo
carcinomas—have been described,[47] although adenocarcinoma and alveo
carcinoma are common distally and oat cell is common in the proxim
airways. Some central bronchial carcinomas may be metastatic from a sm
undiscovered primary carcinoma lying peripherally in fibrotic lung. Conv
tional techniques including tomography and bronchography may not reveal
primary malignancy in an area of severe distortion until the mass is huge (s
Chapter 2, Section 5). Hemoptysis is not a symptom of uncomplicated pulm
nary fibrosis and should indicate the need for an intensive investigation
exclude a neoplasm. A similar problem is seen in scar carcinoma developing
areas of pulmonary fibrosis as a result of systemic sclerosis, sarcoidos
rheumatoid arthritis, and idiopathic interstitial pulmonary fibrosis. Pleu
mesotheliomata may rarely present as localized peripheral masses and may
similar in appearance to a carcinoma. Pulmonary fibrosis sufficient to b
radiographically evident occurs in about 20 percent of pleural mesotheliomat
The incidence of pulmonary fibrosis with peritoneal mesothelioma is greate
since the latter is more often associated with a more intense exposure, esp
cially to crocidolite.[48]

COMPUTED TOMOGRAPHY IN ASBESTOS-RELATED PULMONARY FIBROSIS

Peripheral malignancies are more accurately identified with comput
tomography (CT) than conventional radiography.[49] The author has not re
any report of the accuracy of CT in detecting scar carcinoma in fibrotic lungs.

A description of the physics of computed tomography is beyond the scope of this section. F
those unfamiliar with CT, a good starting point is the articles by G. N. Hounsfield, Computeriz
transverse axial scanning (tomography): Part 1. Description of system, Br J Radiol 46: 1016–102
1973, and J. Ambrose, Computerized transverse axial scanning (tomography): Part 2. Clinical
1023–1047. The technique allows for radiographic differentiation of tissues of different absorptio
capacity to x-rays. It is more than 100 times more sensitive than conventional x-ray systems. T
absorptive capacity of a substance may be expressed in different ways (e.g., the so-called Hounsfi
units, in which on this scale water is equivalent to 0 and bone to +1000, and calcified tissue and bone to
1000 old Hounsfield units). Varying the window width allows for the visual demonstration of o
these tissues with a chosen range of absorptive value. Varying the window level enables the cen

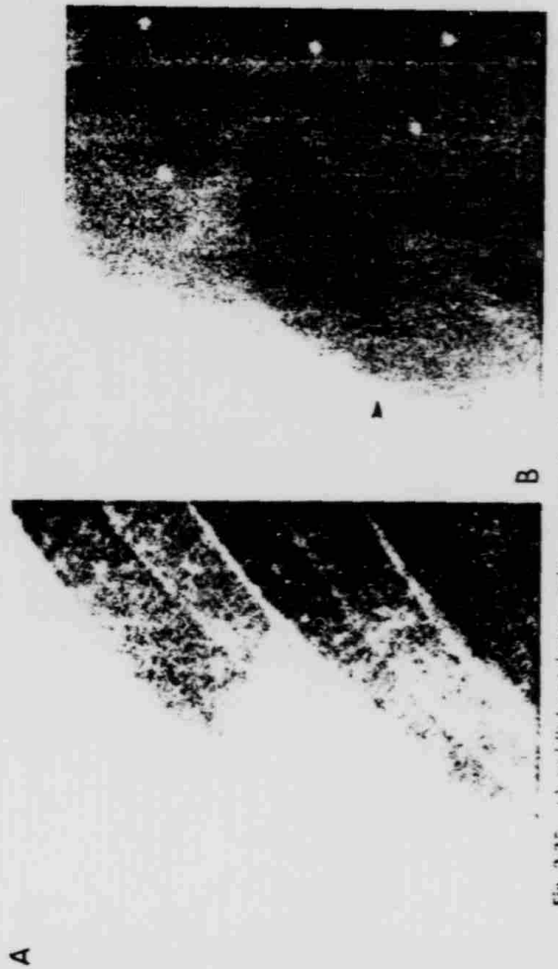


Fig. 2-35. *(A and B) Frontal view and tomogram of patient with alveolar cell carcinoma. A prominent linear fibrotic scar is seen in right upper lobe; the associated cancer is barely seen (A). Tomographic section demonstrates not only the tumor but also a linear plaque adjacent to and parallel to the pleura—as is a radiological marker of prior asbestos exposure.*

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density that appears homogenous on a conventional radiograph may hav
honeycomb appearance on CT examination. At first thought, this might
one away from the diagnosis of malignancy, but this could be erroneous.
carcinomas are multifocal in origin or extend irregularly along preexi
tissue planes. The use of measure mode in the assessment of pulmonary m
is currently being explored. In this technique, the window width is narrow
not the lowest possible, and the window height is manipulated so that
tissue of interest has an equal number of black and white dots. The corresp
ing window height is termed the tissue density and expressed in new or
Hounsfield units (CT No.). CT tissue density is determined by tissue comp
ness (among other factors, e.g., Z number and effective kilovoltage). The v
of this technique in the detection of scar carcinoma is uncertain. A malign
mass, which is a solid compact homogenous entity, should have greater tis
density than a similar x-ray shadow as a result of superimposition of ma
areas of pulmonary fibrosis. It seems improbable, however, that this techni
could differentiate between a multifocal carcinoma arising over a small a
and a malignancy spreading along preexisting tissue planes. CT does hav
part in radiotherapy planning, both in estimation of tissue depth and dose a
in tumor regression during radiotherapy.

Kreel[58] has described CT findings in asbestosis. Large triangular homo
nous dense masses inapparent on conventional radiographs may be seen on
sections (see Figs. 2-36 and 2-37). These have been described with their ba
against the mediastinal surface of the lung in both the lower and middle lob
Their nature is uncertain but probably represents composite shadows due
parenchymal fibrosis and thickening of the visceral pleura.

Transpulmonary bands are bands of soft tissue with parallel borde
unlike the triangular shadows described above) that are present in the costo
phrenic and cardiophrenic angles as well as near the diaphragm; they are n
apparent on routine radiography and again are presumed to be due to fibro
merging with the thickened visceral pleura (see Figs. 2-38 and 2-39).

Aggregates of honeycomb areas in subpleural locations are frequent
seen on CT sections more clearly than on radiographs (see Figs. 2-40 and 2-4
The ease of identification of subpleural fibrotic areas confirms the impressio
from conventional radiography that pulmonary fibrosis begins in subpleur
locations.

In addition to the major changes, nodules of varying sizes comparab

at the selected window width range to be set at any desired point to suit the tissue of interest. Th
for examination of mediastinal fat the window level would be optimal at —40 to 0 Hounsfield un
Measure mode gives an assessment of the absorptive value of the tissue being examined and
hoped that it may be of value in the more precise identification of different types of normal a
abnormal tissue.



Fig. 2-36. *Frontal and lateral tomograms show wedge-shaped areas of pulmonary fibrosis that were inapparent on conventional films of a 48-year-old male with long exposure to asbestos in boiler factory. These tomograms were made because of findings on CT examination (Fig. 2-37).*



Fig. 2-37. *CT examination. Wedge-shaped area of pulmonary fibrosis is in right lower lobe (large arrow), which was not apparent on conventional frontal and lateral chest films. Small arrows indicate mediastinal and pleural plaques.*



Fig. 2-38. *CT examination. Transpulmonary bands of fibrous tissue are seen in the right lung near the diaphragm (horizontal arrow); diaphragmatic plaques on the left are indicated by vertical arrow.*



Fig. 2-39. *CT examination. Section through the upper lobes. Multiple transpulmonary fibrous bands (arrows).*



Fig. 2-40. *CT examination. In the anterior portion of the left lung is a small [illegible] monary band of fibrous tissue (horizontal arrow); slightly lateral are small area[s] nodular densities that were interpreted as fibrosis (vertical arrow); mediastina[l] peripheral plaques are indicated by small oblique arrows. The appearance of the [illegible] lung is due to radical irradiation for a prior adenocarcinoma. Patient is an ex-asbe[stos] worker, who is free from recurrence three years after irradiation.*

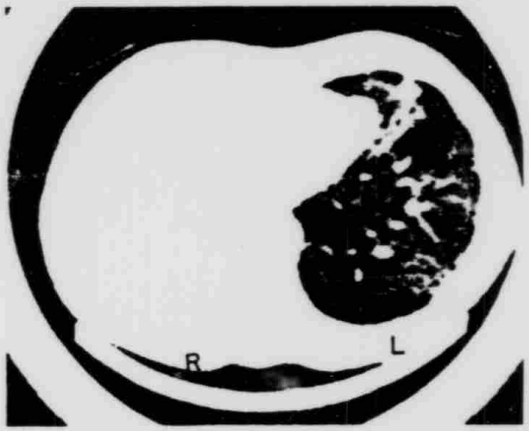


Fig. 2-41. *CT examination. Slightly more inferior than the view in Fig. 2-40. The [illegible] area is more diffuse. On the conventional chest films the differential diagnosis [was] a new primary malignancy, metastases, or focal area of fibrosis was dif[ficult]. An absolute differentiation between pulmonary fibrosis and a malignancy within the tissue planes is still not possible in the CT.*

with the ILO U/C classification of rounded opacities (p less than 1.5 mm; 1.5–3.0 mm; and r, 3–10 mm diameter) and irregular opacities of vary thickness is linear, t medium, and u coarse thickness) may be identified. I when conventional radiography suggest a linear type of fibrosis, CT demonstrate a honeycomb appearance and thus a greater degree involvement.

Parietal pleural plaque appearance with CT is described in Chapte Section 1, but it may be noted that subpleural areas of fibrosis may be s adjacent to noncalcified plaques that are inapparent on conventional radio phy. Similarly, the predilection of the visceral pleura of the lesser fissure show thickening has a counterpart in that homogenous areas of high atten tion with irregular areas may be seen adjacent to the minor fissure. occasion, CT has demonstrated a diffuse symmetrical and bilateral pleu thickening.[51] The cause is unknown, but it may represent the diffuse thicken in the visceral pleura that has been noted at autopsy in some patients.

CT is also helpful in detecting changes in the vascular bed of fibrotic are The vessels may show abrupt tapering and be abnormally straight and thin tortuous toward the periphery. This may also occur in areas without appar fibrosis. Where parenchymal fibrosis is apparent, increased perfusion in more dependent parts as a gravity-related response may be abolished. Thi demonstrated if CT is performed with the patient supine and prone. Cardio cular motion at slow scan speeds make this difficult to detect. Cont enhancement using intravenous injection is unlikely to yield useful informati in this area because of dilution in the pulmonary vascular bed.

CT may show bullae that are inapparent on plain films. Their presence an otherwise healthy asbestos worker may suggest the need for alterna employment, since such patients would have an additional burden sh asbestos-related pulmonary fibrosis develop subsequently.

NONOCCUPATIONALLY RELATED PULMONARY FIBROSIS IN ASBESTOS WORKERS

The syndrome of "a dog with lice and fleas" may be mentioned. Asbe workers may develop pulmonary fibrosis as a result of other causes. Figur 42 is a radiograph of a man with an occupational exposure to asbestos w pulmonary fibrosis was due to histologically proven sarcoidosis. The pul nary fibrosis spares the upper zones, which is unusual in sarcoidosis and a typical of asbestosis. The subaxillary noncalcified plaques are partly obsc by the fibrotic areas. There is thickening of the visceral pleura of the m

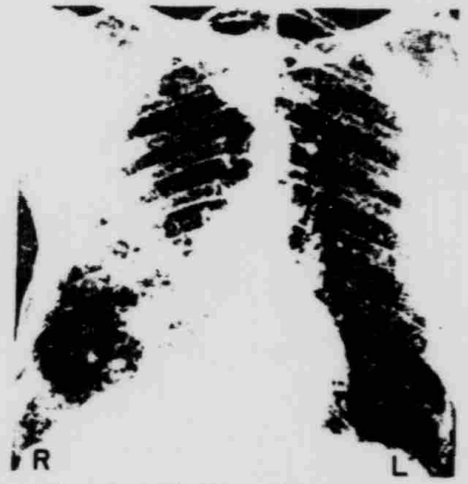


Fig. 2-42. *Sarcoidosis and pleural plaques. There are bilateral thick noncal parietal pleural plaques related to prior occupational exposure to asbestos. Beca systemic symptoms (fever and loss of weight) and rapid onset of lung parenc changes, an open biopsy, which revealed sarcoidosis, was performed.*

fissure. Pleural involvement is rare in sarcoidosis, but visceral pleural thi ing is occasionally seen in asbestos workers. It is never seen in absen parietal pleural changes and may be the residual of a benign asbestos pl effusion. The tissue diagnosis of sarcoidosis may be difficult in such an inst because the presence of "sarcoidlike" granuloma in fibrotic lungs with a h asbestos test load has been reported.[52]

NUCLEAR SCANNING

Nuclear scanning methods are used in the assessment of pulmo fibrosis. The author has not read of its use in asbestos-related pulmo fibrosis. The use of isotopic methods in idiopathic pulmonary fibros described in detail by Roberts et al.[46] Three isotopic techniques are macroaggregated albumin labeled with technetium 99m (^{99m}Tc MAA) to e ate lung perfusion; xenon 133 (^{133}Xe) or xenon 127 (^{127}Xe) to evaluate ve tory functions; and gallium 67 citrate (^{67}Ga) to quantitate lung inflammatio alveolitis.

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SECTION 3
PLEURAL EFFUSIONS

Exudative pleural effusions etiologically related to prior asbestos exposure hav been described in recent years. Assessment for an effusion is now part of th ILO U/C radiographic work chart (Chapter 3). Pleural effusions related t asbestos exposure may be secondary to bronchogenic carcinoma, mesothel oma, cor pulmonale due to pulmonary fibrosis, or so-called benign asbesto effusion.

This additional entity, "benign asbestos effusion," has been described b many authors.[1–3] The criteria for diagnosis are prior history of asbestos expo sure, absence of any other predisposing cause for the effusion, and sponta neous remission of the effusion. Excluded are those patients with an asbesto exposure history and carcinoma, mesothelioma, or cor pulmonale due t severe pulmonary fibrosis or in whom some other identifiable cause such a lymphoma is detectable. Acceptance of the entity of benign asbestos effusion widespread, thus Becklake[4] writes, "The justification for this diagnos increases, and asbestos exposure can reasonably be added to the long list o causes of benign recurrent pleural effusion." Fletcher and Edge[5] state, "Th only occasion when benign asbestos pleurisy with effusion can be diagnose with confidence is when a chronic effusion is persistently negative for tubercu losis on culture, when no other cause can be found, and where the conditio spontaneously improves."

In the author's opinion, the diagnosis of benign asbestos effusion is fraugh with hazard. It cannot be made without a long-term follow-up to ensure tha spontaneous complete resolution of a single or multiple episode of pleurisy ha occurred. Even in such cases, an occult cause such as thromboembolic diseas may be responsible. More worrisome is that an effusion may be present fo months or years, culminating in a diagnosis of mesothelioma. In addition, th pleural cavity in health contains a small amount of pleural fluid, with a protei content similar to that of interstitial fluid. The amount is sufficiently great that i may be demonstrated by lateral decubiti radiographs in 4 percent of healthy persons; this technique will detect amounts of fluid greater than 3–5 ml.[6]

CLINICAL FEATURES

Bearing in mind the author's skepticism expressed above, the following reflects current published descriptions mentioned in the references.

The effusion may be unilateral, bilateral, or recurrent. Regression of a