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Asbestos and the Pleura: A Review

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Asbestos and the Pleura*

A Review

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Key words: asbestos; asbestos production; DNA damage; mesothelioma; plaque; pleura; pleural calcification; pleural fibrosis; public policy; reactive nitrogen species; reactive oxygen species; rounded atelectasis; simian virus-40

Abbreviations: EPA = Environmental Protection Agency; RNS = reactive nitrogen species; ROS = reactive oxygen species; SV-40 = simian virus-40

In spite of the well-recognized health hazards of asbestos and the imposition, beginning in 1971, of increasingly strict exposure limits, the prevalence of patients with pleural abnormalities attributable to asbestos exposure has been increasing. Surveys in the United States and in Europe have shown a doubling of the prevalence of pleural changes, including mesothelioma, between from 1971 to 1975 and 2000.[1–4] Recent very large class-action lawsuits and the bankruptcy of numerous "old-line" industrial companies have been brought to the attention of the public by extensive press reports.[5,6]

Misconceptions about asbestos are legion, and are largely attributable to a lack of awareness of the extended latency—the interval between initial exposure and subsequent biological consequences—that varies from a year or so for some cases of pleural effusion to ≥ 40 years for mesothelioma. Among the public there is widespread anxiety, based on the misunderstanding that a casual exposure, such as walking by a demolition site or entering a schoolhouse that is being repaired, represents a significant health risk to the passerby or to the school child. General concern has been heightened recently by events such as natural disasters or terrorist attacks that produce very high levels of dust. Asbestos diseases are generally dose dependent. Because of difficulties in quantifying exposure, the variable persistence of asbestos fibers in tissue, differences in elapsed time from first exposure to the manifestations of asbestos-related disease, plus interindividual differences in susceptibility to disease, a "safe" exposure level, one that does not cause a specific disease, remains controversial. In the United States, the exposure limit is 0.1 fibers per cubic centimeter.

It is at the pleural surface where the effect of past asbestos exposure is most often found. There are four types of benign pleural reactions: (1) effusions; (2) plaques, local areas of fibrosis of the parietal pleura; (3) diffuse pleural fibrosis, extensive visceral pleural fibrosis, often with fusion of both pleural surfaces; and (4) rounded atelectasis that occurs when an area of visceral pleural fibrosis extends into the parenchyma and renders a portion of the lung airless. There is also mesothelioma, a primary malignancy of the pleura (and occasionally the peritoneum). Other consequences of asbestos exposure are asbestosis, which is fibrosis of the lung parenchyma, and bronchogenic lung cancer.

Asbestos fiber exposure differs by many orders of magnitude between those occupationally exposed and members of their families; those engaged in other types of work in factories, construction, machine maintenance, or mining; and people who reside near asbestos processing facilities or major industrial users. Those who live and work in rural settings are generally considered as not exposed, provided there are no significant asbestos deposits in the local terrain, which may not always be known. These different types of exposure have been categorized as primary (occupational), household (family members of the occupationally exposed),[7] bystander (those working near insulation installers, for example), and environmental (naturally occurring sources).

This report is a survey of historical information, clinical findings, illustrations of salient radiologic findings, current studies in pathogenic mechanisms, and public policy implications of asbestos exposure. Additional information regarding specific features of asbestos-related disease is available from the selected list of references.

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History, Mineralogy, and Geography

From the dawn of the Christian era, there have been sporadic references to objects or materials with unique fire-resistant properties that were both mystifying and bordered on the supernatural. Cloth woven from asbestos fibers, and known as "stone wool," is described in ancient writings as magical because it could be tossed into a fire and removed intact.[8] The word *asbestos* is derived from a Greek term for inextinguishable or unquenchable, and first appeared in the English language in the late 1300s (Oxford English Dictionary). In the 1700s, asbestos-based items such as wicks for oil lamps, asbestos fabrics for conversion into items of clothing, and the production of asbestos-based papers first appeared, but not until the mid-1850s did industrial production commence. The industrial revolution and the widespread adaptation of steam power caused a dramatic increase in demand. Large deposits of asbestos were first located in Canada and South Africa. In the nineteenth century, additional sources were found in Italy, Russia, China, and the United States. Canada is currently the major supplier in the world.[9]

In 1876, Henry Johns of Brooklyn, NY, patented a stovepipe covering composed of asbestos, paper, and felt. Fire was a major hazard at the time, particularly in crowded urban centers, and the fire-resistant properties of asbestos-based materials made them a desirable commodity and Mr. Johns' (later Johns-Manville) enterprise highly successful. The use of asbestos increased progressively in the first half of the twentieth century with an additional rapid escalation during and following World War II (Fig 1). As the adverse health effects became known, exposure controls were imposed by regulatory agencies. In the United States, the initial exposure limit was established in 1971 at 5 fibers per cubic centimeters, reduced to 2 fibers per cubic centimeter in 1976, to 0.5 fibers per cubic centimeter in 1983, and to 0.1 fibers per cubic centimeter in 1994.[10] Thereafter, the use of asbestos declined in this country almost as dramatically as it had increased, from a peak of 803,000 metric tons in 1973 to 16,000 tons in 1998.[9]

A British physician, Dr. Montague Murray, is generally credited with being the first person to diagnose a fatal case of asbestos-related disease, a case of asbestosis. Although his observations were made known to various boards of inquiry beginning in 1899,[11] they were not published until 1907,[12] but not until the 1920s did additional reports began to appear. In 1930, Mereweather and Price[13] published the results of a survey of 363 factory workers in England of whom more than a one fourth had signs of asbestosis. That article firmly established the pulmonary hazards of asbestos exposure. One very significant result of the Merewether report was the adoption of dust-control regulations for Great Britain in 1931.[14] They were not imposed until 1971 in

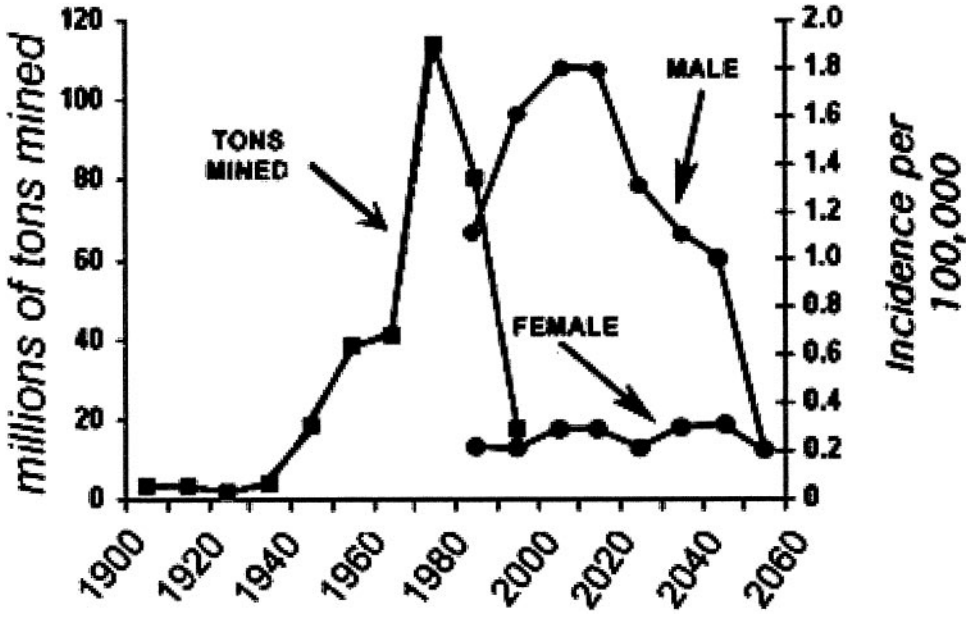

Figure 1. Asbestos production and mesothelioma incidence: asbestos production in the United States in the last century and mesothelioma incidence from 1980 projected to 2055. Asbestos imports are not included and would increase the amount of asbestos used substantially. Reprinted with permission from Price.[4]

the United States. Although the link between asbestos and lung cancer was acknowledged in Germany in 1943,[15] it was not so recognized in the United States until 1955, and not until 1960 was the connection to mesothelioma well established.[16]

The term *asbestos* refers to a group of minerals: crystalline-hydrated silicates that exist in a fibrous form. It is the fiber-like structure, in addition to the chemical composition of the mineral, that is the basis for their extensive commercial use. Asbestos occurs in one of two forms: serpentine and amphibole. Chrysotile is the only serpentine form of asbestos, whereas there are several forms of the amphiboles. Chrysotile fibers are long, curly, and pliable, whereas amphibole fibers are short, straight, and stiff. The major amphiboles that have been used commercially are amosite, crocidolite, and—to a much lesser degree—anthophyllite. Noncommercial amphiboles such as tremolite and actinolite, plus a fibrous zeolite called erionite, are morphologically similar but differ chemically from the commercial amphiboles and are present in substantial concentrations in surface soils in various locations. These include Afghanistan,[17] Bulgaria,[18] Finland,[19] Czechoslovakia,[20] Greece,[21] and Turkey,[22] to cite a few. Significant exposures occur among residents in these regions. In the United States, exposure to tremolite may occur among workers processing, talc,[23] vermiculite,[24] and other products. Ninety to 95% of all asbestos used in the United States has been chrysotile. Because of its chemical and physical properties, the serpentine form of asbestos is most suitable for making fabrics and other flexible items. The amphiboles have superior chemical and physical stability and have been used to make asbestos-cement pipe, floor tiles, and—when mixed with chrysotile—a vast array of friction products, gaskets, roofing, insulation, and fire-proofing materials.

Exposure, Clearance, Tobacco, Latency, Threshold

Asbestos fibers enter the body either by skin contact, ingestion, or inhalation. When raw asbestos fibers were handled with impunity, "asbestos corns" sometimes developed in workers, localized areas on the hands with exuberant epidermal overgrowth due to the intracutaneous deposition of asbestos fibers. This manifestation of asbestos exposure is now solely of historical interest. For the public at large, asbestos is harmless if swallowed. In municipalities with asbestos-cement pipe for water distribution, and a much higher concentration of asbestos fibers in the drinking water than in communities with other types of pipe, no differences in the frequency of asbestos-related diseases were found.[25,26] However, workers with a heavy industrial exposure probably swallow large quantities of asbestos fibers, and this could contribute to the development of peritoneal mesothelioma.

At the present time, essentially all adverse effects on health from asbestos are due to the inhalation of fibers in concentrations sufficient to overwhelm the normal pulmonary defense and clearance mechanisms. Airborne fibers are carried along in the inspired air stream and impinge on the mucous lining of the smaller bronchioles. Tissue fiber burdens are generally related to cumulative exposure.[27] Chrysotile fibers are less harmful than the amphiboles, in part because they are broken down and removed from the lung.[27] Animal studies[28,29] clearly show that cigarette smoke increases asbestos fiber deposition.

Asbestos-related diseases have lengthy latent periods, except for pleural effusions which can occur within a year to $\geq$ 20 years after first exposure[30,31] (Fig 2). Brief but intense exposures are quite capable of causing disease, but it may be many years, with either continuing or no further exposure, before they become manifest. The longest latent periods, $\geq$ 40 years, occur with mesothelioma. Whether or not there is a threshold level of asbestos exposure that does not increase the risk of malignancy is controversial.[32–35] Mesothelioma and lung cancer rates vary by many orders of magnitude between those with a heavy, lifetime occupational exposure and the unexposed (see "Mesothelioma" section). Low-level exposure, as encountered in public buildings, probably does not represent any additional health hazard beyond what is incurred breathing outdoor air.[36,37] However, reliable information about long-term, low-level exposure is exceedingly difficult to obtain.

Pleural Effusion

Pleural effusions due to asbestos exposure vary from a completely asymptomatic event, with either total resolution or a blunted costophrenic angle as the only residual evidence, to an active, inflammatory pleuritis with fever, pleuritic type pain, and a substantial accumulation of bloody pleural fluid. The symptoms do not differ from those associated with other forms of acute pleuritis, including some dyspnea. The erythrocyte sedimentation rate is often elevated, but an elevated body temperature is unusual.[38] The effusions are usually unilateral, but may be bilateral and occasionally subside on one side only to recur on the other.[31] Pleural fluid eosinophil counts exceed the normal in about one third of the patients.[31] The fluid usually conforms to the criteria

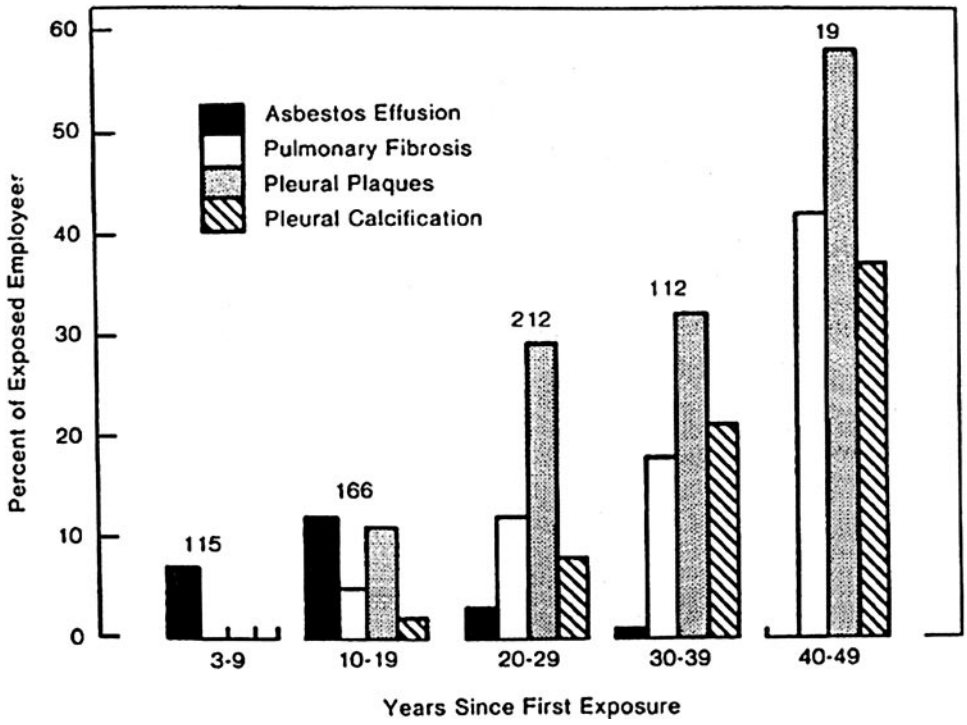

FIGURE 2. The latent period: pleural changes in 624 asbestos-exposed industrial employees. The different manifestations are shown in relation to the time that has elapsed since first exposure. The number at the top of each group of columns represents the number of workers with the latent intervals listed along the bottom of the chart. Reproduced with permission from Epler et al.[30]

of Light[39] for an exudate. Asbestos bodies (asbestos fibers enveloped by an iron-containing protein coat) are seldom[40] or never[41] found in the pleural fluid, may be seen occasionally in pleural tissue, and are frequently present in the underlying lung tissue.[40]

The most sensitive imaging modality for visualizing pleural fluid is the CT scan of the chest. MRI is useful for distinguishing lesions of the chest wall and visceral pleura from fluid accumulations, but it is of limited use in the evaluation of patients with free-flowing pleural fluid.[42]

An unexplained pleural effusion should be sampled for chemical, bacteriologic, and cytologic analysis. Unless the findings are diagnostic, and absent contraindications, a biopsy should be performed. A pleural effusion can be attributed to asbestos only when there is a history of asbestos exposure and all other causes, particularly a malignancy, have been excluded. This requires an observation period of 2 to 3 years. A left-side predominance has been noted in 11 of 15 cases in one report,[43] and in 40 of 73 effusions that occurred in 60 patients in another report.[31] The effusions usually subside slowly and spontaneously over a period of several months.[44]

Asbestos pleural effusions have no specific prognostic implications with respect to the subsequent development of pleural plaques or mesothelioma. Effusions are frequent in the early stage of mesothelioma, and can be very difficult to distinguish from a benign effusion. In one series of 22 patients with an asbestos pleural effusion and follow-up intervals of as long as 17 years, there were no cases of mesothelioma.[38] In another group of 12 patients, mesothelioma developed in only 1 patient 9 years after his first documented effusion.[45]

PLEURAL PLAQUES, CIRCUMSCRIBED

Circumscribed or localized pleural plaques are considered by some as benign markers of prior asbestos exposure, whereas others believe they cause functional impairment, indicate an immunologic deficiency, and are a harbinger of a future malignancy.[46–48] Circumscribed plaques are discrete areas of fibrous tissue limited to the parietal pleura, whereas diffuse pleural thickening or pleural fibrosis is much more widespread and usually extends into the costophrenic angles; additionally the visceral and parietal pleural surfaces are often fused. Both types of pleural thickening are relatively acellular and can coexist.

Plaques are often incidental chest radiographic findings. They occupy irregular, discrete areas on the parietal pleura. The area involved may be barely

visible (Fig 3, *right*, *C*), or plaques may cover much of the parietal pleura and the superior surface of the diaphragm (Fig 4, *center*, *B*, and *right*, *C*). On gross inspection, plaques have a white, shaggy appearance, originate from the inner surface of a rib, and extend across adjacent intercostal muscles. Asbestos bodies are not generally found in plaque tissue, but asbestos fibers that lack the protein envelope may be visible.[49]

Small plaques are often difficult to discern, particularly if the radiographic technique is less than optimal. Chest radiographs best suited to reveal parenchymal detail are often suboptimal for visualization of the pleura, particularly in obese patients. Some radiologic survey results are based on a single posteroanterior image; others include lateral and/or oblique radiographs that may reveal plaques not visible on the posteroanterior view. Survey results also depend on whether radiographic interpretations were made by a single or by a panel of readers. Current survey results, if based on digital radiology[50] or CT scans of the thorax, cannot be compared with older data based solely on conventional radiographs. Ultrasound has no role in identifying pleural plaques, although it is very useful in locating pleural fluid. MRI can be helpful in identifying rounded atelectasis,[42] but it is of limited value in defining plaques or diffuse pleural fibrosis.

The frequency with which pleural plaques occur in different population groups varies widely. They are invariably found in a much higher proportion of male than female patients, and with increasing frequency with advancing age.[51] In a large autopsy series[51] from a hospital serving a region of Glasgow, Scotland, near major shipyards plaques were identified in 51.2% of men $\geq$ 70 years old. This is in all likelihood due to the extremely slow rate at which plaque formation progresses (Fig 5), the number of years of occupational and possible environmental exposure without the benefit of respiratory protection or air quality controls, and the age of the patient cohort. The dose-response relationship for plaque formation is highly variable given the wide range of fiber levels found in lung tissue and the uncertainties regarding exposures. Plaque detection is uncertain using standard chest radiographs. A substantial proportion of plaques subsequently found postmortem[52] or by CT scanning[23] are missed, and the inverse is also true: plaques reported by the radiologist may not be found on autopsy. This is due in part to the erroneous interpretation of images produced by subpleural fat deposits, old rib fractures, and muscle bundles.[53] Subpleural fat creates uniform, smooth, bilateral, and symmetrical opacities, whereas pleural plaques are irregular and, although often bilateral, are rarely

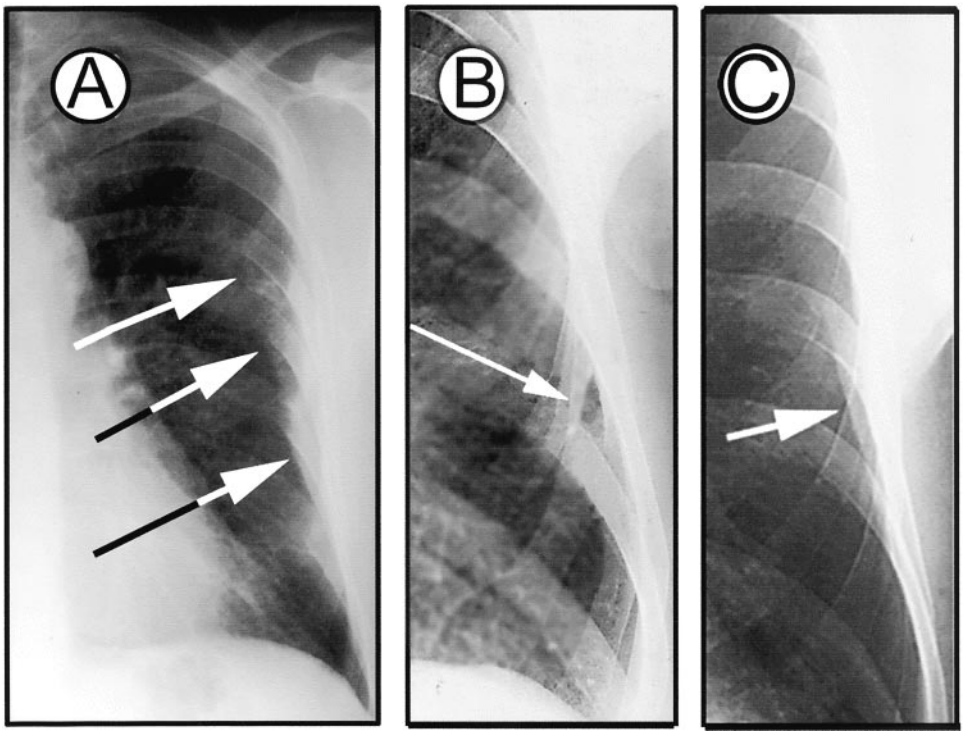

FIGURE 3. Lateral chest wall plaque and some similar radiologic findings due to other causes. *Left*, *A*: Serratus anterior muscle bundles. *Center*, *B*: External oblique muscle slip. *Right*, *C*: Minimal lateral chest wall plaque. This closely resembles a rib companion shadow. These shadows are due primarily to fat and also to muscle tissue that overlies the peripheral pleura.

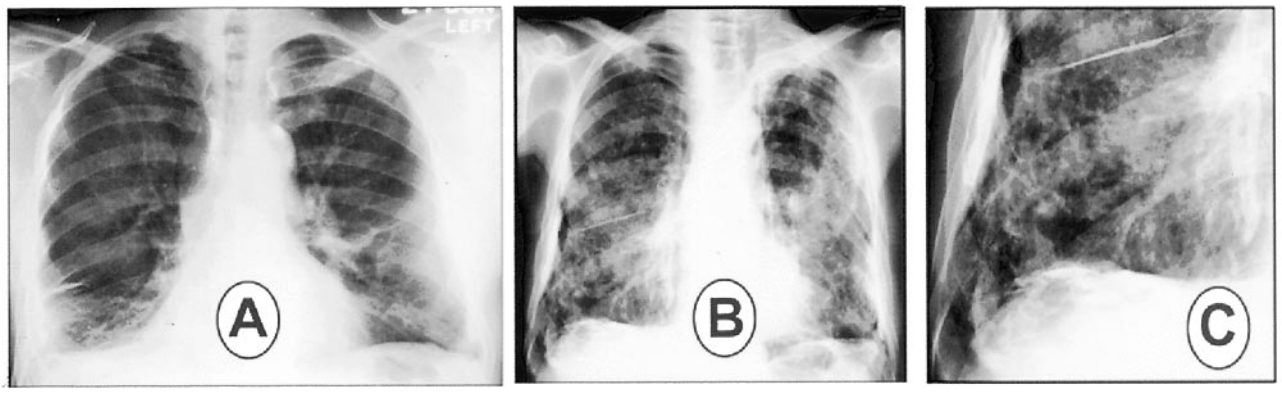

FIGURE 4. *Left*, *A*: Diffuse pleural thickening or pleural fibrosis. Note the costophrenic angle blunting, the interlobar pleural thickening, and the extension of the pleural fibrosis into the apex on the left side. *Center*, *B*: Very extensive pleural plaques with calcification of the pleura on the lateral chest wall, in the minor fissure and on the diaphragm. The costophrenic angle is spared. *Right*, *C*: Close-up view of the lower half of the right hemithorax of *center*, *B*.

symmetrical. They generally develop in the lower two thirds of the thorax and on the outer two thirds of the diaphragm. Serratus anterior and external oblique muscle slips may be misinterpreted as plaques, but they are oriented in an oblique manner opposite to the usual direction of pleural plaques (Fig 3). Companion shadows (Fig 3, *right*, *C*) due primarily to fat tissue are frequently confused with early, localized pleural plaques. High-resolution CT scans are far superior to any other method for imaging pleural plaques. With digital films, and particularly with CT scans, film contrast and density can be adjusted for optimum visualization of the pleural surfaces.

A classification system for rating chest radiographs for the pleural and parenchymal abnormalities of pneumoconiosis, known as the International Labor Organization system, was developed as a tool for epidemiologic studies. Although not intended for the purpose, it is also used for diagnosis. A set of standard reference radiographs, against which a worker's film is compared, is required.[54] An assessment of film quality is also required. Poor quality films are much more likely to be interpreted as abnormal than good quality images.[55] Interobserver agreement is also dependent on the prevalence of abnormalities in the population under surveillance. Agreement is good for normal radiographic findings; variability between readers is increased substantially with abnormal radiographic findings.[55]

Areas of pleural thickening confined to either the anterior or posterior thoracic surfaces differ from lateral chest wall plaques in their radiologic appearance. Plaques on the front or rear thoracic surface are designated *en face* (face on) plaques. They have a maximum density laterally with a gradual diminution and disappearance of their opacity in a medial direction, and may be confused with underlying parenchymal opacities. On a posteroanterior chest radiograph, *en face* plaques that are sufficiently "mature" to have some calcification may have a characteristic coiled or serpentine margin, creating an appearance that has been likened to the edge of a holly leaf and also to the appearance of wax that has hardened after running down the shaft of a burning candle (Fig 6). Diaphragmatic pleural plaques have a variety of contours, but a classic example is a protuberance resembling a mushroom cap, shown in Figure 5, which is virtually diagnostic of prior asbestos exposure. On the other hand a thickened interlobar pleura, primarily between the right upper and middle lobes, has a similar appearance whether it is due to asbestos, prior infection, or any other cause.

Calcium deposition occurs in pleural plaques of long standing. It is unusual among workers with a < 30-year interval from time of first exposure.[30] Fine, punctate, irregular nodules (Fig 6) are an early sign. The flecks of calcium gradually coalesce with the formation of dense streaks or plate-like deposits. Calcification may be limited to a 1- to 2-cm strand or extend over large areas including the diaphragm. In the absence of an alternative explanation such as previous trauma, surgery, or significant pulmonary infections, a calcified plaque on the diaphragm is virtually pathognomonic of prior asbestos exposure.

The impact of circumscribed plaques, with or without calcification, on lung function has been the subject of numerous reports and conflicting findings. Jones et al[56] reviewed 36 studies conducted between 1965 and 1988. Multiple reasons, including differences in radiologic methods and variability in lung function testing, were cited as explanations for the disparate outcomes. Furthermore, confounding factors such as cigarette use, prior pulmonary ailments,

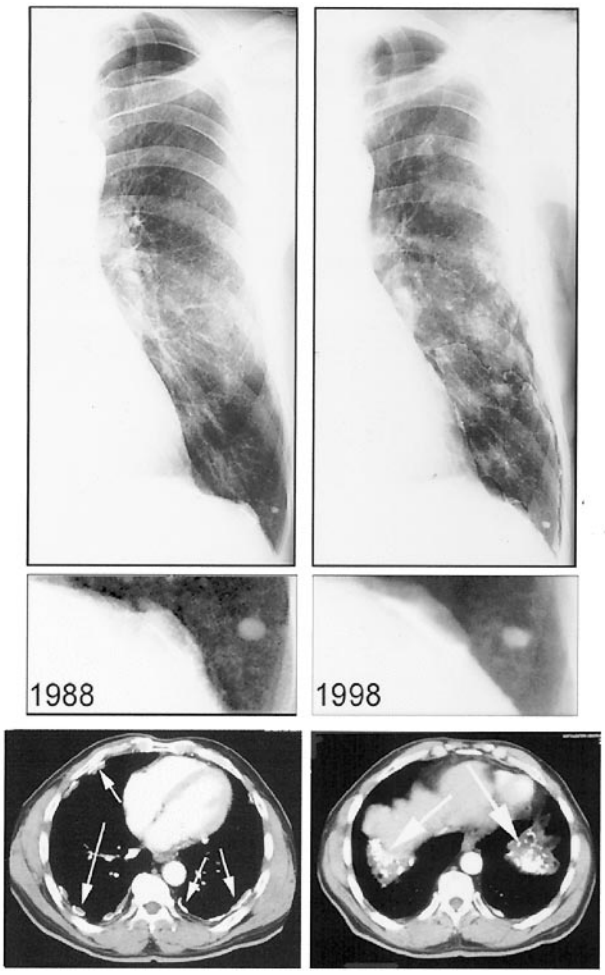

FIGURE 5. Pleural and diaphragmatic plaques. Changes in the size and shape of pleural plaques, and in their calcification occur very slowly. Note the "mushroom cap" shape of the diaphragmatic plaque. The CT scan (*bottom panels*, different patient) may show extensive pleural changes that are not otherwise evident. There are multiple sites of pleural thickening and calcification in the mid-lung region (*bottom*, *left*) and on the diaphragm (*bottom*, *right*).

and other occupational exposures were sometimes either overlooked or not known. Subsequent to the report by Jones et al,[56] approximately 41 additional studies were published in the English language through 2001. Although more sophisticated techniques for identifying pleural plaques and for measuring lung function have been used in most of the recent surveys, and there has been better control for potential confounders, the outcome variation persists. Chest CT scanning, now a part of almost all radiologic studies, provides better identification of pleural abnormalities, and an alternative method (other than the carbon monoxide diffusing capacity) for determining if some lung fibrosis (asbestosis) is present. A restrictive ventilatory impairment, attributed to a mechanical limitation of lung motion, was reported in some studies of patients with circumscribed plaques. However, Schwartz et al[57] concluded, from their studies using high-resolution CT scans and evidence of lymphocytic alveolitis identified by BAL, that parenchymal inflammation and fibrosis are the basis of the restrictive impairment. Since extensive plaques may obscure underlying fibrosis that can only be visualized with CT scans, conclusions based on studies done prior to the availability of this imaging modality may be questioned. However, CT scan interpretations are subjective, the subtle changes that occur with minimal asbestosis are ill-defined, and conclusions based on CT scan findings have also been questioned.[58,59] From their analysis, Jones et al[56] concluded that limited or circumscribed pleural plaques have no clinically significant adverse impact on pulmonary function. In a recent review, Rockoff, one of the authors of the Jones report, and others[60] reach quite an opposite conclusion. In their current view, impaired lung function can be detected by a combination of CT imaging and the use of exercise tests. The impairment would not be apparent with previously used methods of disability evaluation.

Whether pleural plaques augment the likelihood of mesothelioma or other malignancy developing has been evaluated in numerous studies, but with far from consistent results. Edge[61] found a two-fold–greater risk of dying from lung cancer among 425 exposed workers with plaques than in the population at large. A contrary result was reported by Harber et al,[62] who found no link between plaques and asbestos-associated malignancies among 1,500 asbestos-exposed workers followed up for 4 years. Weiss[63] reviewed 13 reports; among the 10 reports he deemed suitably designed to reach a meaningful result, he did not find an increased rate of lung cancer when pleural plaques were present. However, plaques are markers of asbestos exposure, and asbestos is a recognized carcinogen. Lung injury that is not discernable on the chest radiograph, or by other means, could exist and thereby increase the likelihood that a malignant disease will develop.

Pleural thickening unrelated to asbestos exposure is commonplace. It is frequently seen at the lung apices, generally due to prior fungal and/or tuberculous infections. It is unusual for asbestos to cause apical pleural thickening.[64] Obliteration of the costophrenic angle is also commonplace, and is indicative of prior infection, cardiac failure, trauma, other causes, or a previous pleural effusion, possibly an asbestos effusion. At the present time, the preponderance of the evidence indicates that plaques do not increase the cancer risk, but this is far from a universal view.

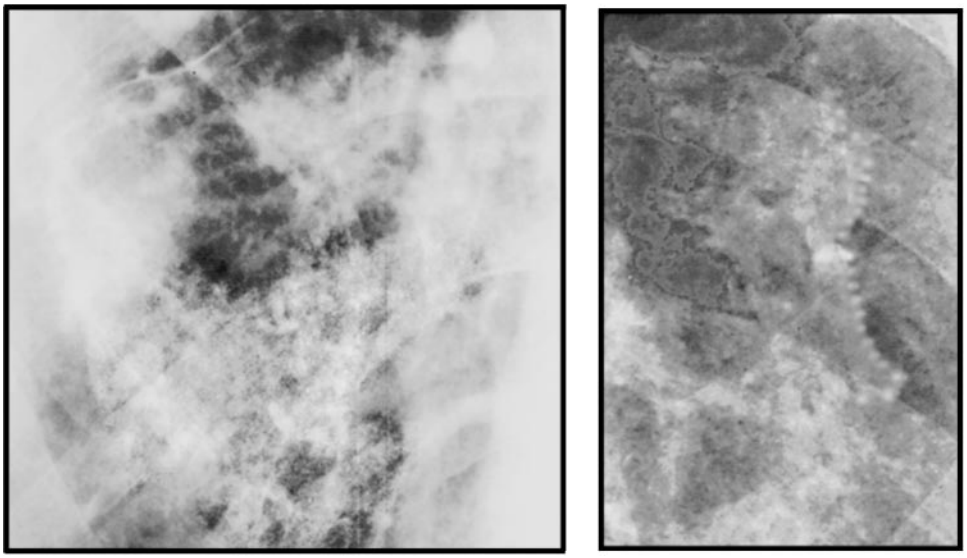

FIGURE 6. *Left*: Punctate calcification in a chest wall plaque. *Right*: Serrated edge of a chest wall plaque.

DIFFUSE PLEURAL THICKENING AND DIFFUSE PLEURAL FIBROSIS

There is general agreement that diffuse pleural thickening, unlike circumscribed thickening or plaques, can cause significant restrictive ventilatory impairment.[56,57,65] Lilis et al[66] reported seven such patients, of whom five succumbed from pulmonary failure that was attributed to a severe restrictive ventilatory deficiency. The hallmark of diffuse pleural thickening is involvement of the visceral pleura, with blunting of the costophrenic angle the most frequent radiologic clue. Localized or circumscribed plaques do not extend into this region. The pleural shadows often extend up both chest walls, usually with some irregularity (Fig 4, *left*, *A*). Methods for measuring the area and thickness of abnormal pleura using CT scans and correlating those results with abnormal lung function have been reviewed by Copley et al,[67] who found an inverse relationship with the FVC ($r = -0.66$ to -0.72, $p < 0.001$) depending on the method used to define pleural thickening. However, in a number of their patients, and also among some of the subjects in other, similar studies,[68] there was a reduction in the carbon monoxide diffusing capacity, which suggests that the reported reductions of lung volumes were not due solely to an abnormal pleura but also to some parenchymal fibrosis.

ROUNDED ATELECTASIS

An unique form of pleural thickening is known as *rounded atelectasis*, *folded lung*, *Blesovsky syndrome*, and by its major radiologic feature: the comet tail sign. This type of pleural involvement is much less frequent than circumscribed plaques or diffuse pleural fibrosis. It has the appearance of a round, mass-like opacity and develops at one, occasionally at several, locations in the pleura with a characteristic curvilinear "tail" extending toward the hilum (the comet tail).[69] Because it may resemble a peripheral tumor, a thorough evaluation of the patient may be necessary. The chest CT and MRI are very useful for visualizing what often presents as an indistinct pleural based mass. If serial chest radiographs are available, the nature of the mass should be apparent. How rounded atelectasis develops is unclear, but a possible mechanism is noted in the legend to Figure 7. Other mechanisms have been suggested and include the regional shrinkage of connective tissue fibrous strands at one location in the visceral pleura,[71] and the subsequent development of adhesions between two parts of the lung following an effusion or infection. When the acute process subsides, the adhesion persists with distortion and obstruction of the bronchus resulting in atelectasis of the distal lung. Most patients with rounded atelectasis are asymptomatic, but they may become symptomatic if the atelectatic volume is large and lung function is compromised.

MESOTHELIOMA

Mesothelioma is usually, but not always, related to the cumulative dose, to the specific mineral form of asbestos fiber, and to the elapsed time from first exposure. The incidence of this tumor has been

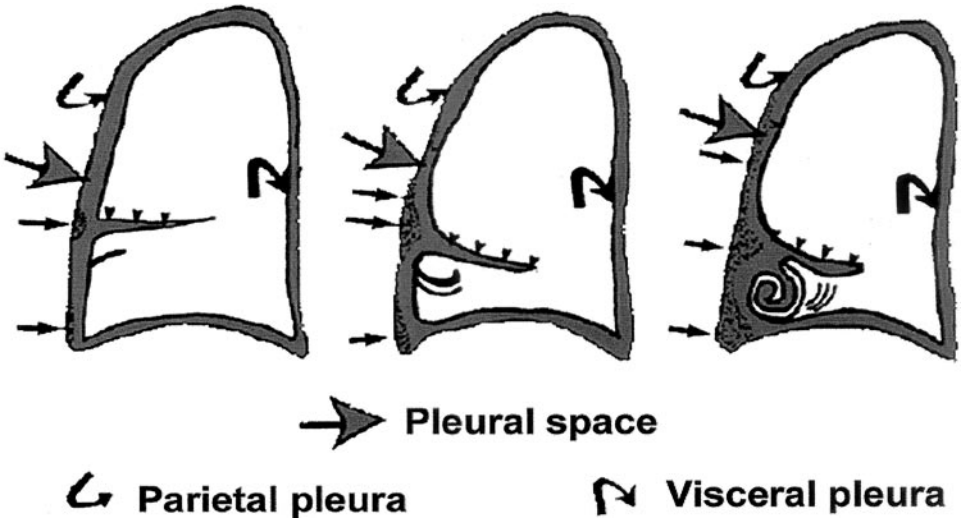

FIGURE 7. Formation of rounded atelectasis. A possible mechanism whereby this occurs is a low-grade inflammatory pleural reaction at one site, fusion of the two pleural surfaces with progressive thickening at the fused region. This results in compression of the underlying lung and bronchial occlusion that renders the underlying lung airless. The bronchus and adjacent blood vessels contribute the "tail" or comet sign of this unusual form of pleural fibrosis.[70] See text for description of alternate mechanisms.

increasing for many years, roughly parallel with the increase in the use of asbestos (Fig 1), but with a lag time of 25 to 40 years. The incidence among female subjects is 2 per million per year, but between 10 per million per year and 30 per million per year in unselected male populations.[72] Among heavily exposed workers, the mesothelioma rate is as high as 366/100,000 person-years,[73] whereas the rate in low-to-moderately exposed workers is almost 80% less (67/100,000 person-years).[2] Whether a minimal threshold exists below which exposures are harmless is uncertain. Exposure to amphibole fibers is much more likely to produce a mesothelioma than chrysotile fibers.[74] Mesotheliomas following exposure thought to be limited to chrysotile have been attributed to tremolite contamination.[74] The greater carcinogenicity of the amphiboles may be due in part to their greater biopersistence and their iron content, which can catalyze the production of reactive oxygen radicals (H_2O_2 and OH^-; see "Pathogenesis" section).

Although significant past asbestos exposure can be identified in many if not most cases of mesothelioma, the tumor also occurs in the absence of known exposure. Mesothelioma has been reported in patients following radiation therapy,[75,76] chronic pleural inflammation,[77] and chemical carcinogens.[78] From 10 to 20% of all mesotheliomas are primary in the peritoneum.[79,80] It occurs rarely in unusual locations, such as the pericardium, tunica vaginalis testis, and female genital tract.[81] Familial malignant mesotheliomas have been described.[82]

These observations have prompted investigators to seek causes, other than asbestos, such as a genetic component or viral exposure. Prior to 1963, simian virus-40 (SV-40) was an unrecognized contaminant of polio vaccine, and therefore it is present in a substantial number of adults.[82] SV-40 large T-cell antigen (Tag) DNA sequences have been found in as many as 20% of patients with mesothelioma without known asbestos exposure and in nearly 50% of patients with definite exposure.[80,82,83] The same DNA sequences have also been found in patients with colon cancer, osteosarcoma, brain tumors, and other cancers.[84] Furthermore, mechanistic studies reveal that human mesothelial cells are uniquely susceptible to SV-40–associated infection, transformation, and immortality.[85,86] Mesothelial transformation by SV-40 is in part due to the capacity of SV-40 Tag to inactivate the tumor suppressor proteins, p53, and p-retinoblastoma family members.[82,87] However, the causal role of SV-40 in the pathogenesis of mesothelioma is controversial. The molecular basis of asbestos-mediated disease is under active investigation to determine the interaction between fiber physical characteristics, free radicals, alteration in proto-oncogene/tumor suppressor genes, and SV-40 expression with the formation of a malignant clone of cells. Understanding these interactions may also provide insight into pulmonary fibrosis, bronchogenic lung cancer and other pulmonary diseases

The initial clinical presentations of patients with mesothelioma are usually chest pain and dyspnea. Less often the first symptoms are nonspecific com-

plaints such as malaise, weight loss, cough, and fever. Most patients will be male (3.6 to 1) and 50 to 70 years of age given the latent interval previously noted.[88] The symptom onset is usually insidious but relentlessly progressive, although it may take the rare patient ≥ 1 year before a diagnosis can be established.[89,90] Physical examination and chest radiograph findings consistent with a pleural effusion are found in 80 to 95% of patients.[91] Ten to 29% percent of patients have little or no fluid, and fluid accumulation diminishes with advanced disease.[88] On a standard radiograph, the fluid may appear to be free flowing and indistinguishable from an effusion due to heart failure or other nonmalignant diseases, but it eventually becomes loculated. Tumor masses often create a lobular appearance along the margins of the fluid. The tumor may "anchor" the mediastinum so that it fails to shift away from the fluid toward the opposite hemithorax. The CT scan provides much greater sensitivity than the usual posteroanterior chest radiograph for identifying fluid and visualizing pleural-based masses, lymph nodes, blood vessels, and lung parenchyma that may be obscured by the fluid. MRI may be useful for distinguishing between chest wall, pleural, and peripheral parenchymal lesions.[92] Positron emission tomography scanning can be helpful for differentiating benign from malignant effusions, and identifying nodal or other metastases that are not otherwise apparent. Distant metastases are infrequent. The tumor gradually fills the hemithorax compressing the lung and airways (Fig 8).

It is mandatory that pleural fluid—and in most cases some pleural tissue—be removed to establish a diagnosis. The diagnostic yield from cytology varies from 25 to 33% of patients. This is increased modestly with the addition of closed-needle pleural biopsy with 21 to 77% positive results.[89,93,94] Exploration of the pleural space with a rigid medical thoracoscope is diagnostic in up to 90% of patients with a pleural effusion.[95] Video-assisted thoracoscopic surgery is supplanting other diagnostic procedures because it provides both a high diagnostic yield and partial staging of the tumor.[89,94] Tumor tissue extends through the needle tract or thoracoscopy site in approximately 20% of patients,[89] but radiation, either prior to the biopsy or subsequently, provides good local control. Immunohistochemical staining of the biopsy tissue is often necessary for definitive identification because of the visual similarities between adenocarcinoma and mesothelioma. Malignant mesothelioma is characterized by staining for calretinin (88%) and vimentin (58%), while adenocarcinomas typically lack these markers and are positive for carcinoembryonic antigen (84%), CD15 (77%), and Ber-EP4 (82%).[96] Electron microscopic examination of tissue is most useful for making the

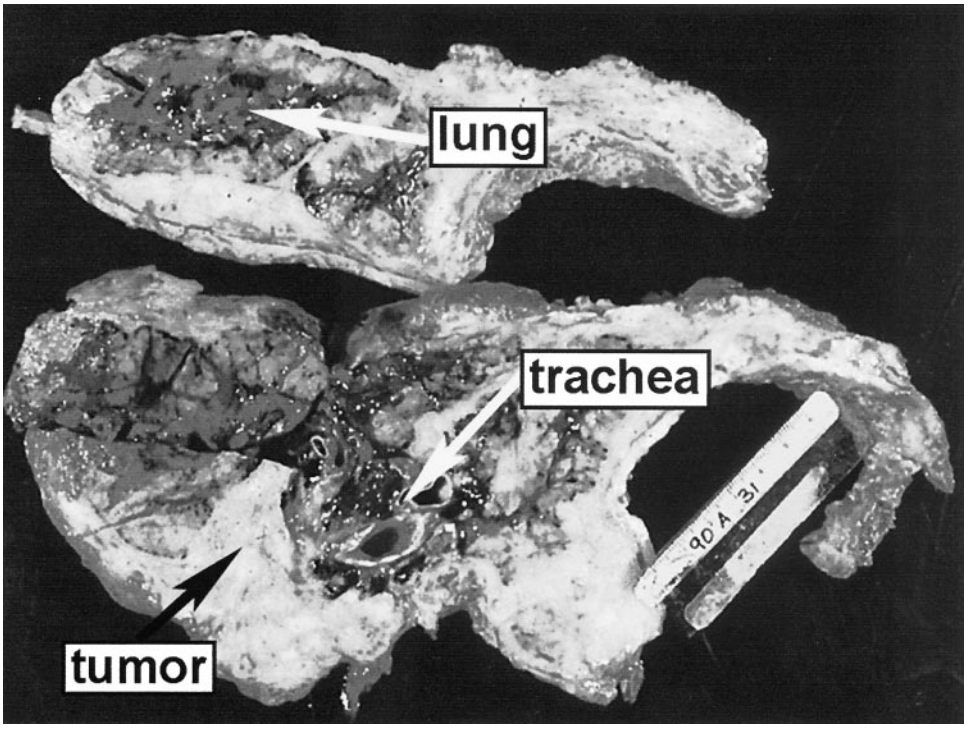

FIGURE 8. Mesothelioma. Note the extent to which the lungs have been compressed by expanding tumor tissue that also extends into the chest wall.

distinction and also for determining the tumor subtype. There are three histologic types of mesothelioma; their distribution among 819 cases was as follows: epithelioid, 50%; sarcomatous or mesenchymal, 16%; and mixed, 34%.[88] The epithelioid subtype has the best prognosis.[89]

Five separate staging systems for mesothelioma are described in a recent book.[97] The newer schemes include some clinical features in addition to the anatomic site and extent of the tumor. Favorable factors in one study were as follows: no more than 5% body weight loss at the time of diagnosis; tumor confined to the parietal pleura, epithelioid cell type, and tumor confined to the ipsilateral pleura, lung, and pericardium.[94] A favorable outlook has been noted among patients with good performance status, young age, and a platelet count $< 400{,}000/\mu L$.[83,89]

There is no widely accepted treatment regimen for malignant mesothelioma that has been proven superior to palliative care. Numerous case reports attest to the occasional long term survivor, but for most patients the outlook is dismal. Hillerdal[88] reported a survival of only 27% of 284 unselected patients at 12 months. At the present time, multimodality therapy utilizing various combinations of chest surgery, chemotherapy, and radiation have been effective in selected patients. The surgical options include pleurodesis, pleurectomy, and extrapleural pneumonectomy. Radiation therapy—either external beam or intracavitary—and various chemotherapy agents are used.[98]

Pathogenesis

How asbestos fibers that have impacted the airway wall migrate to the pleural surface and, in the case of circumscribed pleural plaques, ignore the visceral pleura in the process is quite obscure. Why asbestos fibers that reach the pleural space induce an effusion in one patient, plaques or diffuse pleural fibrosis in another, or mesothelioma in yet another is equally obscure. An explanation probably lies in some combination of yet-to-be-determined mechanical, biochemical, and genetic events. Detailed reviews of the pathogenesis of asbestos-associated diseases have been published.[80,90,96,99]

One traditional explanation for the formation of circumscribed plaques—mechanical irritation by asbestos fibers protruding from the visceral pleura causing continuous mechanical irritation of the overlying parietal pleura—is very likely incorrect. Inflammatory reactions are not seen at the site of plaque formation, nor are the two pleural surfaces adherent, which would be expected following a local inflammatory process.[100] Alternate routes by which asbestos fibers may reach the parietal pleura include the path of lymph flow and the systemic blood stream. Plaques are said to develop along pathways of lymphatic drainage at sites where there is an uptake into parietal pleural lymphatics.[101] Experimental studies[102] in rabbits indicate that cell recruitment and interaction are important determinants of pleural reactions to asbestos fibers.

There are many features of asbestos fibers that could account for their genotoxic effects on certain cell types. For example, amphibole fibers have a high iron content that can generate reactive oxygen species (ROS) by iron-catalyzed reactions over prolonged periods on the surface of the fiber that is lodged within the lung. ROS can also be generated during frustrated phagocytosis of long asbestos fibers and dissolution of macrophages. In contrast, short asbestos fibers can be successfully phagocytized and incorporated into lysosomes. This phenomenon may explain in part why long thin fibers, *ie*, > 8 μm in length, are more carcinogenic after inhalation or injection into the pleura or peritoneum of rodents.[37,103] Asbestos fibers activate inducible nitric oxide synthase in alveolar macrophages and in lung epithelial cells that may generate reactive nitrogen species (RNS).[104,105] Both ROS and RNS can cause mutagenic oxidative lesions.[105] Other indicators of genetic damage, including chromosomal changes, alteration of cell cycle progression, formation of aneuploid and polyploid cells, and nuclear disruption by long fibers, have been demonstrated in cell culture.[106] However, it is difficult to determine whether these signs of genetic damage are relevant to asbestos-associated carcinogenesis or to cell death, since in some studies high levels of asbestos exposure were utilized.

Apoptosis, regulated physiologic cell death, is crucial for organ development and host defense.[107,108] All forms of asbestos can induce DNA damage, which is a potent stimulus for apoptosis. ROS derived from asbestos fibers induce DNA damage and apoptosis in relevant lung target cells including mesothelial cells.[109,110] There are multiple additional sources of ROS once cells are exposed to apotogenic stimuli.[111] The antioxidant catalase and deferoxamine—an iron chelator—reduce mesothelial cell apoptosis, which is additional support for the role of iron-derived ROS in tumor formation.[110]

The inhibition of normally functioning tumor suppressor genes and/or activation of proto-oncogenes are considered a prerequisite to subsequent tumor promotion, characterized by perpetuation of genetically altered cells and establishment of a tumor. Proto-oncogenes and tumor suppressor genes have been implicated in the development of mesotheliomas, although none have as yet been shown to be

essential to tumor formation in humans. p53 is an important transcription factor that regulates the cellular response to DNA damage, and in turn determines whether cells undergo apoptosis or a proliferation blockage, thereby allowing time for DNA repair and cell survival. An important role for p53 in the pathogenesis of mesothelioma is suggested by the finding that heterozygous $p53^{+/-}$ mice have a greater number and earlier onset of asbestos-induced mesotheliomas compared with wild-type mice.[112] Cell-signaling events may be linked to the advent of cell proliferation preceding tumor promotion and establishment. Cell signaling is initiated by asbestos fibers either through the generation of ROS/RNS, or by an interaction of asbestos fiber and growth factor receptors on the cell membrane. Fibers that are highly carcinogenic (erionite, crocidolite) are potent inducers, contrary to a number of other nonpathogenic fibers and particles, of early response proto-oncogene expression such as c-fos and c-jun.[113] How these proto-oncogenes interact with various growth factors is under active investigation.[80] Some growth factor antagonists are presently being assessed in lung cancer treatment clinical trials in the United States and in other countries.

Public Policy, Past and Present

It seems ironic that following the initial imposition of asbestos fiber exposure limits in the United States at 5.0 fibers per cubic centimeter in 1971, followed by successive reductions to 0.1 fibers in 1994,[10] that the number of claims for asbestos-related injury has increased dramatically. Claims filed with just one of the trusts established to compensate injured workers increased from a few hundred per year in 1980 to 1983, to 68,000 in 2000 (D.T. Austern, Esq; personal communication; September, 2002). This increase is due to multiple factors including the large number of workers who were exposed in the 1940s and in subsequent decades, the lengthy time interval between exposure and onset of disease, and insufficient scientific information on which to base well-reasoned public policy. Prior to setting and then reducing asbestos fiber exposure limits, there were the customary public hearings; unlike the usual regulatory procedures, general interest in asbestos regulation was intense, aided in part by widespread publicity, Environmental Protection Agency (EPA) pronouncements, and conflicting medical and scientific opinions. For example, at one time it was the position of the EPA that a single asbestos fiber could cause cancer.[114] The ensuing public outcry and demand for the removal of asbestos from public buildings, particularly schools, was intense, costly, and ill-advised (see "Exposure, Clearance, Tobacco, Latency, Threshold" section). A "third wave" of asbestos-related morbidity and mortality among the general public due to asbestos exposure in public buildings was predicted by some, but subsequently rejected (see Mossman et al[34] for a summary of this controversy) following studies demonstrating the similarity of asbestos fiber concentration in the indoor air of buildings with asbestos in place and in outdoor air.[115] Further, long-term occupants of public buildings containing asbestos insulation had no greater prevalence of asbestos-related chest radiographic abnormalities than similar occupants of asbestos-free buildings.[116] Disagreement about the safety of chrysotile fibers also clouded the issue.[34] Twenty years after the "one fiber" pronouncement, the then EPA director, W. K. Reilly, acknowledged that it was government ". . . responsibility for the misperceptions that have led to unwarranted anxiety and unnecessary asbestos removals."[114] Asbestos-containing materials, in both public buildings and private homes, should be left in place, covered, or sealed, and examined periodically to ensure physical integrity. Remodeling or demolition of structures with asbestos in place, no matter how well sealed or covered, requires special precautions plus proper containment and disposal of debris.

Many additional factors have contributed to the massive number of asbestos-related cases that confront our courts. Some examples are as follows: radiologic evidence of asbestos exposure in the absence of any clinical or measurable functional impairment; "emotional harm," justified in part on the extended latent interval from time of exposure to manifestation of disease; the costs of future medical monitoring, which has not been proven useful for detecting diseases for which there is no treatment and that may never occur; and conflicting opinions regarding the significance of pleural plaques. The aggregate cost of awards, based on such tenuous claims, can be substantial and has already driven many defendants into bankruptcy.[117] When this occurs, the truly sick and deserving cannot be compensated.

A change in the method of compensation—one based on objective measures of lung function and on radiologic findings—was proposed but not adopted.[118] Because the resources available to compensate the disabled are rapidly diminishing, and to relieve the logjam of claims clogging various legal jurisdictions, there have been renewed efforts to develop objective criteria, such as published standards for disability assessment as the basis for settling claims for nonmalignant types of asbestos diseases.[119] Legislation has or will be proposed to mandate disability assessment as the basis for settling claims for nonmalignant

asbestos diseases.[119,120] The prospects for passage now seem favorable because of support by both some plaintiff and defendant attorneys.

Physicians responsible for the care of patients with asbestos exposures may be drawn into the medical-legal arena. Detailed clinical records, complete laboratory test results, and biopsy or other interventions when appropriate and indicated will enable the treating physician to confidently meet any legal inquiry.

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