

# Asbestos related disorders

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An updated summary of current understanding of asbestos related disorders is presented, along with a review of the history of the disorders, and the mineralogy, biological tissue burden, pathogenesis, pathology and clinical aspects of the asbestos related disorders, with particular emphasis on important information for the clinician.

**Key Words:** Asbestos, Asbestosis, Asbestos pleural diseases, Mesothelioma

FROM THE BEGINNING OF THE 20TH CENTURY, SEVERAL diseases have been associated with asbestos exposure. Some have a definite association whereas others initially considered to be associated with asbestos exposure were afterwards proven not to be. The following are unequivocally recognized as asbestos related diseases.

*Asbestosis* – an interstitial fibrosis of the lung parenchyma;

*Benign asbestos pleurisy* – also called benign pleural effusion, an exudative and transient inflammation of the pleura;

*Pleural plaques* – accumulations of collagen fibres forming hyaline masses that are avascular, acellular and circumscribed, usually limited to the parietal pleura;

*Pachypleuritis* – accumulations of collagen fibres forming hyaline masses that are avascular, acellular and diffuse, affecting the parietal and visceral pleura, occasionally invading the interlobular spaces of the lung parenchyma, which has been called ‘crow’s feet’ and is not to be confused with asbestosis;

## Maladies de l'amiante

**RÉSUMÉ :** Les auteurs présentent une mise-à-jour des connaissances actuelles des affections reliées à l'exposition à l'amiante, revisant l'histoire de ces affections, la mineralogie, la métrologie, la pathogénèse, la pathologie et les aspects cliniques de ces affections reliées à l'amiante, en insistant sur les informations les plus intéressantes pour le clinicien.

*Rounded atelectasis* – an effect of asbestos-induced pleural disease that is caused by the scarring of the pleura and adjacent lung tissue, with retraction of the scar tissue and partial collapse of adjacent lung tissue;

*Bronchogenic carcinoma* – a malignant bronchopulmonary tumour similar to that associated with cigarette smoking and other lung carcinogen exposures;

*Malignant mesothelioma* – a malignant tumour of the mesothelium of the pleura, that is usually fatal within 12 to 24 months after clinical diagnosis.

Benign nodules in the lung parenchyma are occasionally seen in asbestos workers. They can be benign lymphoid nodules, scars of localized fibrosis or more strikingly rounded atelectasis.

Diseases not accepted unequivocally as related to asbestos exposure will not be discussed here; readers are referred to an exhaustive review (1).

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## HISTORICAL ASPECTS

Asbestos, from the Greek ασβεστος, meaning ‘inextinguishable’, has been known since antiquity. It was initially used for the wicks of torches in temples, and from 2500 BC in pottery. In the time of the pharaohs, Herod noticed that asbestos linens were used for the incineration of corpses. Charlemagne stunned his guests by throwing his asbestos table cloth on the fire to clean it. Asbestos was the Salamander wool of alchemists (2).

Asbestos use remained on a small scale, related to crafts, until the discoveries of the vast deposits of Quebec and Russia at the end of the 19th century. In Quebec, exploration of a mine started in 1878 at Asbestos, a small township named by its product and where chrysotile, the white asbestos, has been produced ever since. In Russia, commercial production of chrysotile started in 1885. In South Africa crocidolite blue asbestos was initially produced in 1880, and amosite and anthophyllite became commercially available in the First World War.

The world production of asbestos increased slowly at the beginning of the 20th century to reach a total amount of  $5 \times 10^9$  kg by 1930. Rapid acceleration of production in the following years resulted in a yearly production of  $5 \times 10^9$  kg, responding to the demand for its use in some 3000 applications. Twenty years after the industrial use of asbestos began in Europe, Auribeault (3) in 1906 described 50 cases of pulmonary fibrosis in an asbestos textile factory in Normandy, France, while in England, Murray (4) described the first case of asbestosis in a 30-year-old asbestos worker, the last survivor of a group of 10 employed in the same workshop. Also in 1906, Marchand (5) first described asbestos bodies. After 1926, it became accepted that asbestos was toxic for the pleura, lung and airways.

The huge problem posed by the industrial use of asbestos on public health and hygiene became clear in the 1950s. In 1955, Jacob and Bohling (6) reported on calcified pleural plaques; in 1960, Wagner et al (7) described 33 cases of malignant mesothelioma, of whom 28 were exposed to crocidolite asbestos from South Africa. In the following years, animal experimentation confirmed the fibrosing and carcinogenic potential of all types of asbestos fibres.

In the 1960s and '70s, large epidemiological studies by several American and European teams were presented at international conferences in New York in 1964 (8), 1979 (9) and 1990 (10); at the International Agency for Research on Cancer (IARC) in 1972 and 1979 (11); in Montreal in 1980 (12); in Cardiff, Wales in 1986 on the biological effects of chrysotile (13); and in Paris in 1991 on malignant mesothelioma (14).

In the 1980s, studies on the biological mechanisms of asbestos related diseases were initiated in several laboratories around the world (15-17), which have increased our understanding of the pathogenesis of the disease processes.

## MINERALOGY

The term asbestos refers to a family of naturally occurring, flexible, fibrous hydrous silicate minerals that are relatively indestructible and heat resistant. For the mineralogist, the

**TABLE 1**  
**Classification of asbestos minerals**

Asbestiform	Nonasbestiform	Chemical Formula
Chrysotile	Antigorite, lizardite	Mg <sub>3</sub> (Si <sub>2</sub> O <sub>5</sub> )(OH) <sub>4</sub>
Crocidolite	Riebeckite	Na <sub>2</sub> Fe <sub>5</sub> (Si <sub>8</sub> O <sub>22</sub> )(OH) <sub>2</sub>
Amosite	Cummingtonite-Grunerite	(Fe,Mg) <sub>7</sub> (Si <sub>8</sub> O <sub>22</sub> )(OH) <sub>2</sub>
Anthophyllite	Anthophyllite	(Mg,Fe) <sub>7</sub> (Si <sub>8</sub> O <sub>22</sub> )(OH) <sub>2</sub>
Tremolite	Tremolite	Ca <sub>2</sub> Mg <sub>5</sub> (Si <sub>8</sub> O <sub>22</sub> )(OH) <sub>2</sub>
Actinolite	Actinolite	Ca <sub>2</sub> (Mg,Fe) <sub>5</sub> (Si <sub>8</sub> O <sub>22</sub> )(OH) <sub>2</sub>

term asbestos is part of the morphological terminology to describe a property known as ‘crystal habit’, used to describe the fibrous aspect in which some minerals crystallize. The characteristics of this ‘crystal habit’ are the high ratios of length to breadth (aspect ratio), flexibility, similarity to organic fibres, the small diameter of elementary units (elementary fibrils) that can be associated longitudinally to form bundles of fibres or, in less oriented aggregates, due to variations in mineral content and different forms of the component crystals.

Although more than 30 minerals show asbestiform crystallization, only six minerals are of industrial use: chrysotile, crocidolite, amosite, anthophyllite, tremolite and actinolite (Table 1). Asbestos related diseases have been reported in association with exposure to all types of asbestos fibres; the incidence of various diseases and the intensity of the pathological processes vary with the different types of fibres.

**Chrysotile:** Chrysotile fibres result from a peculiar hydro-thermic transformation (serpentization) of ultrabasic rocks, a group that also includes lizardite and antigorite. The crystalline structure of serpentines is complex but their chemistry is simple, being hydrated magnesium silicates with some iron as a substitution element. Chrysotile fibres are relatively translucent with a silky sparkle. Depending on the mine of origin, they have more or less flexibility. The elementary fibrils have an average diameter of 0.03 µm and are grouped to form an open core cylinder with layers of intertwined fibrils forming an onion-peel structure around the core. Each tube is about 20 nm in diameter; the tubes are grouped in slivers 0.1 mm<sup>2</sup> which contain  $20 \times 10^6$  tubular fibrils, in a relatively parallel orientation.

Chrysotile is of commercial interest because of its mechanical properties of resistance to heat and traction, and its flexibility, adsorbancy, chemical resistance to alkalines, and the ease with which it may be spun for textile products. It has a weak resistance to acid, but resists other chemicals and heat over 100°C, and loses its structure above 575°C.

**Amphiboles:** The amphibole asbestos group contains several minerals, similar in structure but distinct in chemical composition. The asbestiform structure of the five amphiboles differs slightly from that of chrysotile, as it is more rigid, does not form a cylindrical structure but runs in chains of silicate tetrahedra. This chain-like structure is stacked lightly, which permits good cleavage. Because of their rigidity, amphiboles form fewer aggregates than chrysotile, fibres are more read-

ily seen in aerosols, generate more fibre dust and are more resistant to acid and heat.

*Crocidolite* is a sodium iron silicate formed in thermally metamorphosed banded ironstones. It is often referred to as blue asbestos, and has been mined in South Africa, Australia and Bolivia. It is not as harsh as amosite and has been used in spinning and insulation. It is reputed to be the most dangerous due to its strong association with mesothelioma.

*Amosite*, mined only in the Transvaal area of South Africa, is an iron magnesium silicate. Brownish in colour, amosite has the longest fibres but its harshness renders it unsuitable for spinning; it has been used mainly for heat insulation.

*Anthophyllite* is a white amphibole, a magnesium silicate containing various quantities of iron. It occurs in fibrous masses with short fibre bundles. It was mined and used in Finland until 1970.

*Tremolite* is a white amphibole, a green yellow calcium and magnesium silicate that is mined in relatively pure form in Italy and Japan and is a common contaminant in most chrysotile mines.

Specialized references can be consulted for further details (18,19).

## ASBESTOS PRODUCTION AND USES

The world production of asbestos increased until 1975 to 1980 when production reached some five million tons of the material per year. It has now stabilized at about four million tons per year.

The development of an asbestos mine usually starts with an open pit operation where mechanical shovels and bulldozers work to break down the rock for transportation of the raw material to a processing mill. As opposed to the traditional underground mining process, open pit operations account for 70% of the total production of asbestos.

The raw material is further processed by fragmentation, sorting and screening operations to concentrate the desired asbestos material and eliminate the undesired ores. The milling process further concentrates the fibre, eliminates undesired minerals, removes grit and dusts, dries and finally separates the fibres into various commercial grades.

At the present time, chrysotile represents 95% of the world production, and the main market is the production of asbestos-cement. Chrysotile is produced mainly in Russia, Canada, Swaziland and Zimbabwe; minor production plants exist in California, Australia, Cyprus, Italy, Brazil and China. Amosite was produced only in South Africa. Crocidolite is produced in South Africa, Australia (now ceased) and Bolivia. Anthophyllite was produced only in Finland.

Asbestos is used in over 3000 applications, of which the major ones are: asbestos cement products, including pipes, shingles, clapboards, flat sheets, corrugated sheets, moulded sheets for the building construction industry; vinyl asbestos floor tile; paper for insulation and filtering products; brake linings and clutch facings; textile products such as yarn, tape, felt, tubing and rope; and spray products for sound, heat and fire insulation.

The major end users in the past have been the building

construction industry, shipbuilding and the automobile and railroad equipment industries, where much of the insulation and friction materials are now made of nonasbestos fibre materials.

The longest asbestos fibres are used mainly in the textile and insulation industries; the intermediate fibres are used in asbestos cement production, and friction and filter production; and the shortest fibres are used in the vinyl-asbestos tile industry and in paints. The mill tailings of the mining process can be used in road construction and for the extraction of magnesium.

## ASBESTOS FIBRES IN ENVIRONMENT AND IN HUMAN TISSUES

In industrial settings, the control of asbestos dust has proven to be the most effective mode of disease prevention, through legislation limiting asbestos dust exposure in the work place below 1 fibre/cm<sup>3</sup> of air. The current American standard is 0.2 fibres/cm<sup>3</sup> of air. In the past, asbestos exposure in the workplace may have been over 100 fibres/cm<sup>3</sup> for some cases and was commonly between 5 and 20 fibres/cm<sup>3</sup>.

To enforce legislation, methods for airborne dust sampling were developed; particles are sampled on a membrane filter and counted under a light microscope at a magnification of 500 times, screening for fibres having a length greater than 5 µm and length to width ratio greater than 3. It remains the method of reference but many chrysotile fibres will not be seen.

Transmission electron microscopy (TEM) can magnify up to 100,000 times but preparation of the specimen is more time consuming and expensive. The method has been a tool of significant impact in environmental air pollution in the neighbourhood of asbestos mills, plants and factories.

For clinical diagnosis, worker's compensation and medico-legal purposes, the search for asbestos fibres in biological samples is increasingly used to document past exposure to asbestos. In that context, analyses of human tissues supplement clinical methods of diagnosis of the asbestos related diseases. Laboratory methods in optical and electron microscopy are available in specialized laboratories (20-22), where samples are first separated by filtration.

Optical microscopy is used to count ferruginous bodies and fibres longer than 5 µm and larger than 0.25 µm in diameter. This method is widely used by pathologists for routine lung pathology, sputum cytology and lung lavage cytology to provide a set of fundamental indices of asbestos exposure. The limitations of optical microscopy are the same as for air sample analyses.

Asbestos fibres and other fibrous particles can be coated by macrophages with an iron-protein coat with formation of bead-like structures on the fibres. They are rarely found on fibres shorter than 10 µm long, and are more associated with amphiboles than chrysotile, possibly because of the greater dissolution and breakdown of chrysotile. These ferruginous or asbestos bodies (AB) can be found in virtually anyone in the population if appropriate methods are used. In cases of asbestos related diseases, they can usually be found in the lung parenchyma. However, they are often not

seen in asbestosis due to chrysotile exposure alone, unless phase contrast microscopy is used after tissue digestion (20-22).

### **Asbestos bodies in lung tissue**

On sputum cytology samples, the control population has no AB, and any AB seen constitutes an index of significant exposure. On lung lavage samples, nonexposed subjects have less than 1 AB/mL of lavage effluent; more than 1 AB/mL suggests lung tissue AB greater than 1/mg dry lung which corresponds to a nontrivial exposure. On lung tissue samples: nonexposed white collar workers have less than 0.1 AB/mg; nonexposed blue collar workers have less than 0.5 AB/mg; blue collar workers with minimal exposure have more than 0.5 AB/mg and less than 2 AB/mg; patients with pleural plaques have in the order of 1.7 AB/mg; patients with mesothelioma have AB within the range of nonexposed to the range of patients with asbestosis; long term asbestos workers with grade 0 asbestosis have up to 1300 AB/mg; long term asbestos workers with grade 1 asbestosis have about 8000 AB/mg; long term asbestos workers with grade 2 asbestosis have about 73,000 AB/mg.

### **Asbestos fibres by optical microscopy in lung tissue**

The general population has less than 250 fibres/mg tissue; exposed persons with grade 0 asbestosis have 2400 fibres/mg; persons with grade 1 asbestosis have 8000 to 19,000 fibres/mg; and persons with grade 2 asbestosis have 14,000 to 200,000 fibres/mg

### **Asbestos fibres by TEM in lung tissue**

The general population has less than 1000 fibres/mg (average 2 to 300 fibres/mg), 90% of which are less than 5 µm in length, and fewer than 100 fibres more than 5 µm long, 70% of which are chrysotile and none are amphibole, amosite or crocidolite; residents of a mining town such as Thetford Mines, Quebec may have 10 times the level found in the general population; patients with pleural plaques have 100 to 5000 fibres/mg; patients with mesothelioma have fibres from within the range of normals to the range of patients with asbestosis; asbestos workers with grade 0 asbestosis have about 2000 to 19,000 fibres/mg; workers with grade 1 asbestosis have about 135,000 fibres/mg; workers with grade 2 asbestosis have about 1,370,000 fibres/mg. Finally, uncoated fibres always outnumber the coated fibres, particularly for chrysotile fibres and in the general population.

### **Deposition and clearance of asbestos**

For the nonfibrous minerals, it is well recognized that particles greater than 10 µm in diameter rarely reach the lung beyond the upper airways and that most particles deposited in the alveoli are less than 5 µm in diameter. However, these considerations do not apply to the fibrous minerals such as asbestos. Fibre deposition in the lung is largely ruled by the fibre diameter, the fibre length having a relatively less impor-

tant effect. Thus fibres 200 to 300 µm in length with a diameter less than 3 µm can be found in the lung. Typical fibre length in asbestos bodies is 20 to 50 µm and many fibres less than 5 µm long can also be found (22).

In animal experiments, it has been clearly shown that the fibres are primarily deposited in the bifurcations of conducting airways and in the alveolar parenchyma (16). The deposition of inhaled fibres is diffuse and extends to the subpleural lung tissue, where the concentration may be markedly elevated.

Clearance of asbestos fibres from the lung occurs by a variety of pathways, including the mucociliary escalator system, translocation into the interstitium and into the lymphatic system and dissolution, degradation, defibrillation and breakdown of the fibre materials originally inhaled. The short fibres are cleared more readily from the lung so that over time the overall mean length of fibres appears to increase. Thus, chrysotile fibres are cleared more rapidly than the amphiboles (22,23). These considerations are of interest in relation to the effects of fibre type, size and length:width ratio in the pathogenesis of asbestos related diseases.

## **ASBESTOSIS Pathogenesis**

The fundamental problem with asbestos fibres in biological tissues (15-17) is related to their toxicity in inducing fibrosis and cancers of the lung and pleural space. In the fibrosing processes, the disease starts as an inflammatory reaction which evolves in a fibrosing repair process, leaving permanent scars. In the cancer processes (24), the disease starts as a multistep process in which the DNA of the target cells suffers increasing amounts of damage – genetic mutations – through a variety of molecular injuries, resulting eventually in tumour cells proliferating over time to a clinically detectable disease. Several experimental studies in animals and studies *in vitro* of cell cultures have documented that all types of asbestos fibres can produce all asbestos related diseases, asbestosis, bronchogenic carcinoma and mesothelioma.

*In vitro* experiments have shown that asbestos fibres (Figure 1) can cause cell membrane damage which, if severe enough, will cause cell death, gene mutation, chromosomal aberration and cell transformation. Asbestos fibres are also capable of inducing macrophages in the lung to produce various growth factors for fibroblasts and other cells participating in the pathogenesis of asbestos related diseases. The mechanisms of pathogenesis are incompletely understood but the general outlines are already developed (21,24).

**Specificities of asbestos fibres: type, dimension, durability and chemical functionalities:** The dose, fibre type, dimension and durability of the fibre with surface chemical reactions will influence toxicity, carcinogenicity and fibrogenicity to variable degrees. The dose-response is well documented epidemiologically and experimentally for the majority of asbestos related diseases. Studies *in vitro* and in animal experiments have shown that toxicity is related to the fibrous nature of the mineral, as demonstrated by the absence

of toxicity of pulverized asbestos or nonfibrous analogues of asbestos. The diameter of the asbestos fibres is important because fibres greater than 3 µm in diameter do not penetrate into the lower lung but those less than 3 µm will penetrate cell membranes and be translocated into the interstitium of the lung and pleural space to cause disease. The length of fibres is also important; the shortest fibres (less than 3 µm) are phagocytosed or translocated to the lymphatics to be drained to the pleural space, whereas fibres longer than 5 µm are incompletely phagocytosed and stay longer in the tissues.

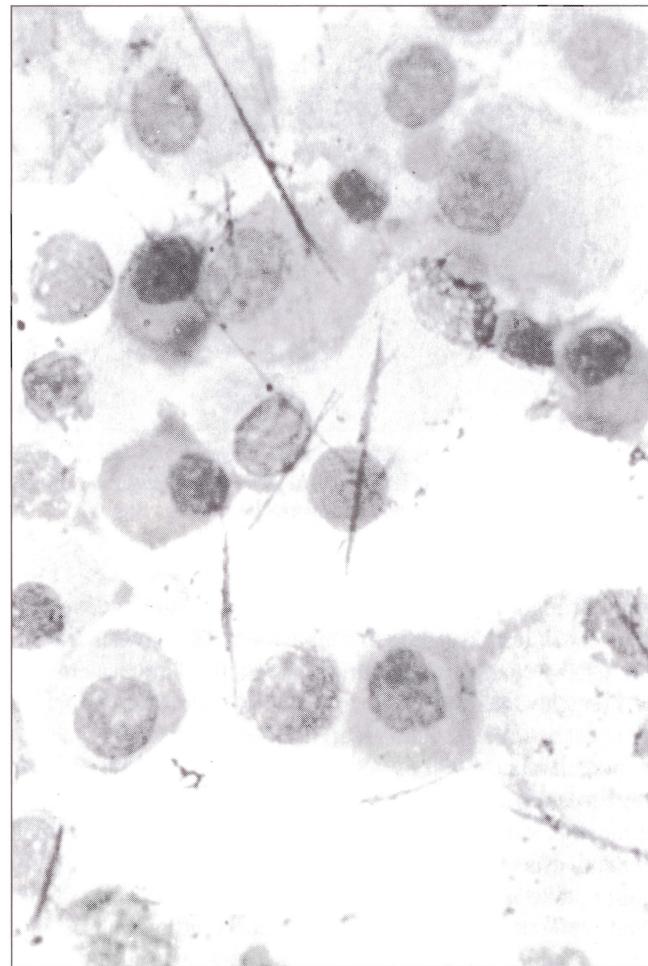
The amphiboles are generally recognized to be 10 times more carcinogenic than chrysotile for the mesothelium; this fact is particularly well documented for crocidolite. Amphiboles are also more prone to induce pleural fibrosis. Lung fibrosis, however, is equally affected by both types of asbestos fibres (23).

The composition of asbestos fibres can influence their toxicity. The relative solubility of chrysotile will attenuate its toxicity whereas its 'splittability' (multiplication effect) will enhance toxicity. Surface properties as well as electrical charges will also influence toxicity. Breakdown of the bonds between atoms on the surface leads to unstable atoms with residual charges which constitute active sites. The adsorption of carcinogens such as polycyclic aromatic hydrocarbons enhance the carcinogenicity of asbestos; similarly, the catalysis of chrysotile can liberate free radicals, which are toxic to cells.

The initial lung injury occurs almost immediately after exposure at the alveolar duct bifurcations, where the terminal bronchioles divide into individual alveolar spaces. In animal experiments, after only 1 h of exposure to asbestos there is active uptake of fibres by the type I epithelial cells, and within 48 h increased numbers of alveolar macrophages accumulate. Although one exposure may not cause asbestosis in all cases, it may be expected that chronic exposure will cause this lesion to progress, forming first a localized peribronchiolar fibrosing alveolitis, followed by diffuse fibrotic scarring. Any increase in asbestos dose exposure amplifies the cellular responses. The initial injury starts a cascade of events in which macrophages flood the site of injury and stimulate the proliferation of fibroblasts.

**Macrophage derived cytokines regulate the disease process:** Fibronectin is a glycoprotein produced by the macrophage capable of recruiting fibroblasts to the site of injury and initiating their proliferation. In lavage fluid, fibronectin is increased significantly only in asbestos-exposed individuals (25), and procollagen 3 (indicating new production of collagen or scar tissue) increases significantly when a fibrotic process is in the early phase and evolves to grade 1 asbestosis. In asbestos workers without clinically evident disease, levels of fibronectin and procollagen 3 in lavage are comparable to controls, but these levels are significantly elevated in those with asbestos associated alveolitis (subclinical asbestosis), or clinical asbestosis.

In addition to fibronectin, alveolar macrophages recovered from patients with asbestosis release exaggerated quantities of cytokines, including platelet-derived growth factor

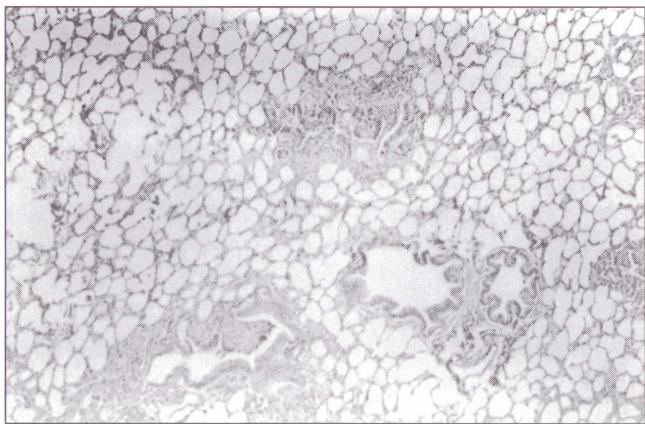


**Figure 1)** Cytospin of a lung lavage in an asbestos worker showing several fibres, many of length greater than the average macrophage diameter (8 µm). Wright-Giemsa stain X740

(PDGF), insulin-like growth factor (IGF-1), and fibroblast growth factor (FGF) (15-17). PDGF, IGF-1 and FGF attract fibroblasts to sites of injury and up-regulate their proliferative activity, leading to the formation of scar tissue.

**Activated macrophages produce tissue damaging molecules:** Damage to the initially injured area is aggravated by macrophages releasing free oxygen radicals, through direct cytotoxicity and peroxidation of cell membranes, to sustain further the inflammatory process (26,27). An additional source of tissue destructive substances comes from the release by the macrophage of plasminogen activator (28), which converts plasminogen to plasmin, a protease which can degrade the interstitial matrix glycoproteins, thus increasing tissue destruction.

**Progression and latency of asbestosis:** The chronic and progressive nature of asbestosis has been documented from the initial subclinical lesion to clinical asbestosis (15-17,25,29) by means of lung lavage, thin section analyses under electron microscopy, thin section computed tomography (CT scan), and <sup>67</sup>gallium lung uptake. Such studies have shown that the inflammation and injury produced by exposure to asbestos fibres is continuous from the time of expo-



**Figure 2)** Asbestosis grade 1 seen in a sheep as peribronchiolar inflammation and fibrosis limited to the surroundings of some of the peripheral airways. Hematoxylin-eosin  $\times 19.6$

sure, through the latent or subclinical phase, to the development of clinical disease identifiable by the classic methods of chest x-ray changes and pulmonary function impairment.

Lung lavage studies have shown the changes that take place at the time of subclinical disease, while CT has shown significant abnormalities in the presence of normal radiography in 20 to 35% of long term asbestos workers without clinical asbestosis. Similarly,  $^{67}\text{gallium}$  scans are abnormal in many asbestos workers without clinical asbestosis.  $^{67}\text{Gallium}$  uptake is a useful indicator of early (subclinical) lung injury long before it is recognized in chest radiographs. Fully 75% of subjects who initially had a positive  $^{67}\text{gallium}$  scan without clinical asbestosis went on to 'full blown' clinical asbestosis over a four-year period (25).

After clinical recognition of asbestosis it is generally accepted that this is often a chronic and progressive disease. Viallat et al (30) studied a population of asbestos workers in a Corsican township when almost 80% of the workers had no radiographic evidence of disease; despite no further exposure, more than half later developed radiographic evidence of disease. Other studies have also documented disease progression after cessation of exposure in animals and in humans. The progression rate at present appears to be closer to 20%, due to decreases in the intensity of exposure associated with improved industrial hygiene and methods of recognition.

**Susceptibility to asbestosis:** It is recognized that when exposure to a toxic substance is well in excess of the tolerance level, the disease will appear in all exposed subjects, as was the case in the British workshop where Murray (4) described his first cases of asbestosis. Such a situation can be easily reproduced experimentally, but in recent years is rarely seen. More often a fraction of the workforce develops disease even when apparently not exposed to higher levels than other workers in similar situations (25,29,31-33). This phenomenon of individual susceptibility has been studied in terms of immunology, of pulmonary structure and of clearance capacity. Human immunohistocompatibility studies, including our own (34), have been unable to find an immunological marker of the human leukocyte group A system which can be asso-

ciated with susceptibility. However, some characteristics of the upper airways have been linked to susceptibility (33) by influencing alveolar clearance of asbestos dust from the lung.

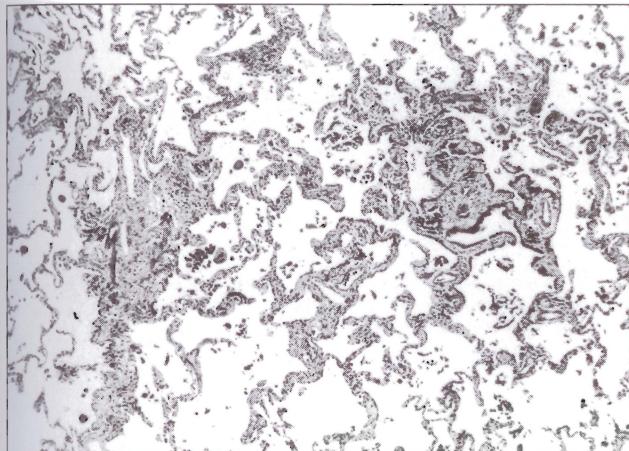
In humans it is not possible to measure directly the lung clearance of inhaled asbestos dust and to relate that to the development of asbestosis, but several independent observations suggest that clearance is linked to the risk of disease (35). First, lung tissue fibre burden has been found to be higher in asbestos workers than in the general population; second, asbestos workers with disease limited to the airways have twice the lung fibre burden of workers without airway disease; third, patients with asbestosis have twice the fibre burden of patients with disease limited to the airways; finally, analyses of lung lavage fibre content of workers with asbestosis are higher than in exposed workers without asbestosis. Studies in the sheep model have been particularly useful in showing a higher level of fibre retention in animals with asbestosis than in those not developing the disease after comparable exposure (35). The longer fibres were particularly associated with this effect. Thus, the individual clearance capacity appears to play a critical role in the susceptibility to develop disease. The relative risk of developing asbestosis for an asbestos worker decreases in proportion to the asbestos fibre dust level in the workplace. Recent reports suggested a 1% risk after a cumulative dose of 10 fibres-year/m<sup>3</sup> of air. This finding contributed to a lowering of the current threshold limit value (level of exposure) to less than 1 fibre/m<sup>3</sup> of air, given the normal 30 to 40 years of work for most asbestos workers.

### Pathology

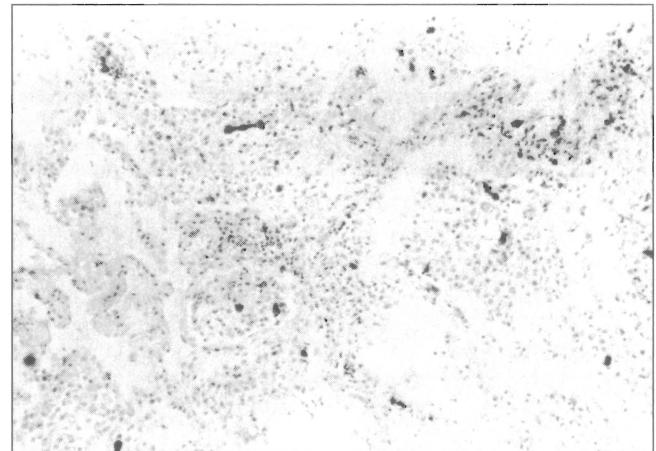
The sheep model of asbestosis has been repeatedly documented to parallel human asbestosis and has been particularly useful in correlating cellular and clinical events (15). Figure 2 shows scarring in and around a bronchiole from a sheep exposed to a single dose of asbestos and sacrificed eight months after exposure. Because of the relative lack of sensitivity of clinical tools, this lesion cannot usually be recognized by routine pulmonary function tests or chest radiography. It is our understanding that only when these lesions cover some 25 to 50% of the airways will there be a measurable change in pulmonary function. Similarly, it is only when the peribronchiolar process becomes sufficiently diffuse (Figure 3, grade 2 or more pathological asbestosis) that it becomes detectable by radiographic methods. Such early lesions have been reported in asbestos-exposed individuals with minimal functional impairment, as judged by standard clinical diagnostic tools. Similarly, studies in subjects suspected of interstitial lung diseases also demonstrated these early lesions. Mildly symptomatic subjects complaining of shortness of breath with normal chest x-rays had pathological evidence of fibrosis. Such lesions are not visible in the chest radiograph because they are not sufficiently widespread.

Exposure of the lung to asbestos dust can initiate one of the following reactions (15).

*A transient inflammatory reaction*, with rapid clearance of the inhaled fibres, most often occurs in subjects exposed very



**Figure 3** Left Asbestosis in a more inflammatory stage with cellular infiltration and asbestos ferruginous bodies. Hematoxylin-eosin x80. Right Asbestosis in a more fibrotic stage with fibrosis around the peripheral airways and extension of the fibrosis into the interstitium between airways. Hematoxylin-eosin x20



occasionally or to very low doses of fibres, who may never develop asbestosis. This is also seen in a large proportion of long term asbestos workers who have no detectable changes related to their asbestos exposure. Experimentally, this type of transient tissue reaction occurring without histopathological lesions has been reproduced in animals (36).

**A low retention reaction.** Asbestos exposed subjects who possess effective clearance mechanisms may have a biological reaction limited to the site of deposition of fibres at the bifurcation of peripheral bronchioles. The fibres initiate macrophage attraction to the site, and an inflammatory reaction which evolves to scar formation limited to the distal airways. This type of lesion has been seen in humans and in animal models.

**A high retention reaction.** This reaction is seen in the most susceptible subjects, who retain the most fibres. The tissue reaction is the most intense and causes a dense accumulation of inflammatory cells, activated macrophages and neutrophils, and fibrosing alveolitis results (Figure 3). The macrophages and neutrophils initiate a cascade of biological events at the site of fibre deposition, sustained by weak clearance of the longest fibres. This high retention reaction is known to initiate asbestosis in humans and in animal models.

Pathologically, asbestosis is a fibrosis of the lung associated with retention of asbestos bodies recognized at optic microscopy, or of asbestos fibres seen by TEM. The definition of asbestosis, upgraded by a committee of the College of American Pathologists, now recognizes both the severity and the extension of the fibrotic process (21,37).

Macroscopically, the lung gross features vary with the severity of the disease process. Early, the visceral pleura loses its transparency and the parenchyma has grey streaks of fibrous tissues in the interlobar and interlobular septa with invasion of lung tissue. In a later phase of disease, the pleural surface has a nodular aspect, quite similar to liver cirrhosis, and the lung parenchyma is characterized by loss of volume, scars and cyst formation, usually prominent in the lower zones.

The College of American Pathologists has defined four grades of severity of asbestosis, now commonly used (37). *Grade 1* – Fibrosis involving the wall of at least one respiratory bronchiole with or without extension into the septa of the immediately adjacent layer of alveoli; there is no fibrosis in more distant alveoli. This is the asbestos airway disease of Churg (21).

*Grade 2* – Fibrosis as in grade 1, plus involvement of alveolar ducts or two or more layers of adjacent alveoli; there still must be a zone of nonfibrotic alveolar septa between adjacent bronchioles (Figure 3).

*Grade 3* – Fibrosis as in grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchi have thickened, fibrotic septa; some alveoli may be obliterated completely.

*Grade 4* – Fibrosis as in grade 3, but with formation of new spaces of a size larger than alveoli, ranging up to 1 cm; this lesion has been termed honeycombing. Spaces may or may not be lined by epithelium.

The pathological description also includes three extension grades based on the proportion of respiratory bronchioles involved by the disease process. Three grades of extension are defined: Grade A – only occasional bronchioles are involved, most showing no lesion; Grade B – more than occasional involvement is seen, but less than half of all bronchioles are involved; Grade C – more than half of all bronchioles are involved.

This approach to the pathological description of the disease process is complete, precise and has been useful in correlation studies of other parameters of disease severity such as radiographs and lung function tests.

### Clinical findings

The symptoms and physical signs of asbestosis are quite similar to those of other interstitial lung fibroses, ie, dyspnea, dry cough and nonspecific malaise. Dyspnea on exertion is the usual presenting symptom, which worsens as the disease progresses with associated loss of lung function. Nonproduc-

**TABLE 2**  
Comparison of computed tomography (CT) scan techniques

Technical aspects	High resolution CT scan	Conventional CT scan
Slice thickness (mm)	1 - 2	10
Algorithm	Os	Standard
Current (mA)	170	140
Voltage (kV)	120	12
Scanning time (s)	2	2
Matrix	512x512	512x512
Visual fields (cm)	20 - 24	30 - 40

tive cough and chest pain are usually present only in some cases, late in the evolution of disease. When cough is productive, it should be considered to be due to a complication such as bronchitis or pneumonia. The chest tightness and pain of patients with asbestosis are attributed to muscle pain, appearing only when dyspnea becomes severe. Hemoptysis is not a usual complaint in asbestosis and should be investigated. The symptoms of asbestosis may occur during the working years or following exposure cessation, as disease may become clinically apparent only after retirement.

Fine crisp nonmobile crepitations are the most important physical findings in asbestosis. They can be heard early in the lower lateral lung fields in the late inspiratory phase, and as disease progresses, they are audible in the lower posterior lung fields and in mid and late inspiratory phases; in severe disease, they are audible throughout inspiration and in all auscultatory fields. Rales are a good physical sign for early detection of disease, often preceding changes in lung volumes and airflow. In most cases, however, rales appear with changes in lung function and chest radiography. Other adventitious sounds are usually absent.

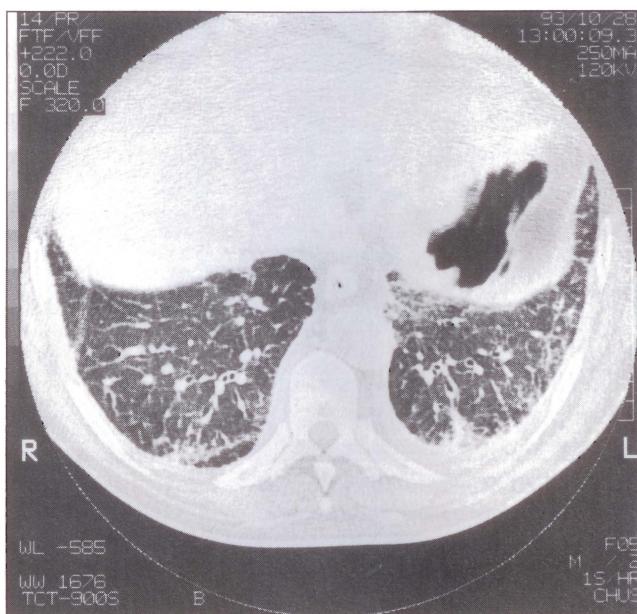
Finger clubbing may be present, but does not necessarily relate to the severity of asbestosis. Cyanosis and reduced chest expansion are late manifestations.

Lung function tests reveal usually a restrictive change associated with mild end expiratory airflow limitation. The restrictive pattern progresses as disease worsens but the airflow obstruction does not worsen as the rigidity of the lungs enhances airflow in the peripheral airways.

### Radiology

The radiological tools used in the diagnosis of asbestos related disorders are the posteroanterior (PA) and lateral chest radiograph, oblique chest films and CT scans of the chest in conventional and high resolution (HRCT) modes (Table 2). The plain standard high kilovoltage PA and lateral chest radiographs are adequate for basic radiological information. Oblique films facilitate recognition of pleural changes and pleural based abnormalities.

The International Labour Organization is an organization that has facilitated the development of an International Classification of Radiographs of Pneumoconioses (38). The goal of the classification is to code abnormalities in a simple and



**Figure 4)** Computed tomography scan of an asbestos worker with asbestosis and bilateral diffuse pleural thickening. In this window of the lower lung field, parenchymal nondependent subpleural densities may be seen

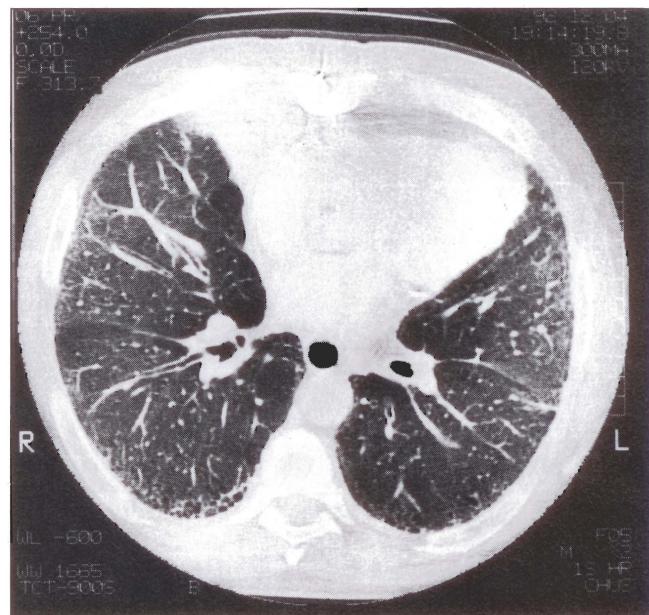
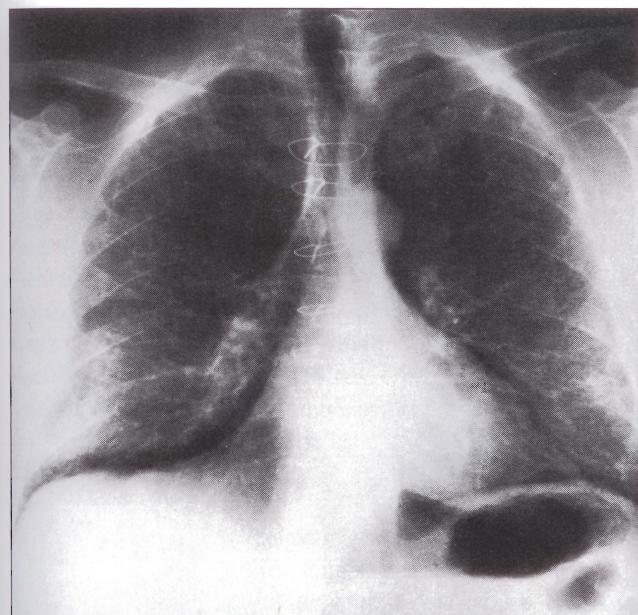
reproducible manner. The organization provides standard reference chest radiographs which are used in the classification.

The CT scan is not justified in the periodical examination of asbestos-exposed workers, but has a place in clinical investigation, in defining pleural changes and in early detection of interstitial lung fibrosis. In lung cancer or mesothelioma, CT scan allows a better definition of the extent of disease, for orientation of diagnostic or therapeutic interventions, and to follow disease progression.

The HRCT can detect discrete abnormalities of the lung interstitium often adjacent to pleural plaques or thickenings. Furthermore, HRCT permits a better appreciation of emphysematous changes and helps to differentiate the contribution of these changes and those of early asbestosis in borderline cases (17,39,40).

The HRCT changes are not pathognomonic but relatively characteristic when the following changes are seen bilaterally on HRCT: thickening of the interlobar and interlobular septa in the periphery of the lung (Figure 4); parenchymal bands extending from the pleural surface in the parenchyma (Figures 4, 5); honeycombing, small cystic zones of lung destruction with thick walls, mostly located in posterior areas and in nondependent areas of the lung (Figure 6); curvilinear lines in nondependent areas, parallel to the pleural surface but located 1 cm from the latter (Figure 7), which correspond either to lung fibrosis that precedes honeycombing or to areas of atelectasis due to local changes close to the pleura or to inflammation; nondependent subpleural densities which are a nonspecific indicator of interstitial lung disease (Figures 4, 5, 6, 7).

Although HRCT can recognize subtle changes of early interstitial lung disease often not visible on chest radiograph,

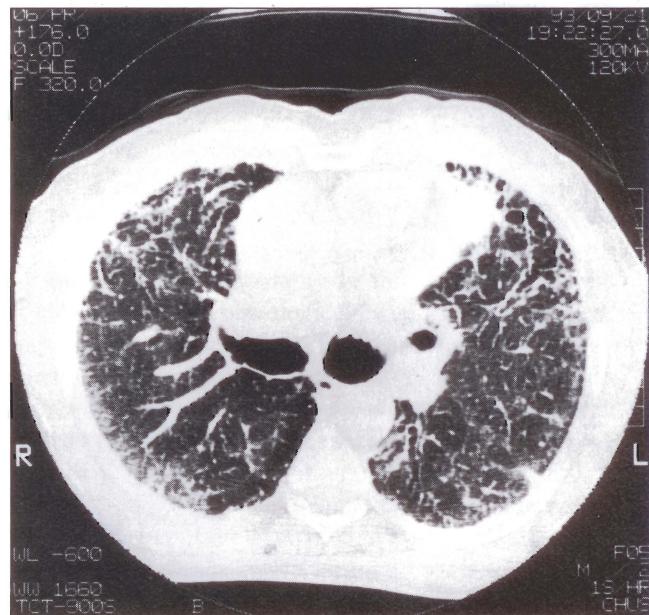


**Figure 5)** Chest radiograph (**left**) and computed tomography scan (**right**) of an asbestos worker with asbestosis, seen as subpleural densities. The diffuse interstitial abnormalities are more prominent

there is currently no technique of imaging that is as sensitive as histopathological examination of the lung, which can detect the disease process within hours after asbestos fibre deposition (16). Pathological changes can be recognized experimentally within days after asbestos exposure, but in human work conditions it takes at least 10 years before changes can be seen on the chest radiograph. Obviously, the pulmonary abnormalities seen on chest radiograph or HRCT cannot be attributed to asbestosis in the absence of pleural plaques and a history of significant asbestos exposure.

On standard chest radiographs, asbestosis is usually manifested as diffuse reticulonodular infiltrates at the lung bases (2,32). Early in the disease process, the abnormalities of the lung parenchyma are seen in the lower two-thirds of the lung fields as fine thickenings in the vascular markings (Figure 8); later the infiltrations become more clearly reticular, better defined in the peripheral lung and extending more diffusely into other lung fields (Figure 9). The changes do not have the clarity of silicotic nodules and can mimic chronic congestion of the lung secondary to left heart failure. In the advanced stage of asbestosis, the radiographic images have the appearance of honeycombing, with coarse infiltrations associated with severe tissue destruction and distortion. All the infiltrates of asbestosis are nonspecific and can be seen in other lung diseases. When the lung changes are accompanied by pleural manifestations of asbestos exposure, the diagnosis of asbestosis is more likely (Figure 10). However, several cases of asbestosis documented pathologically had no pleural changes on chest radiograph and HRCT.

Small nodular opacities, septal lines, linear coarse or fine linear opacities, a ground glass appearance and honeycombing are all seen in asbestosis. Lung volume may be normal or reduced. Progressive massive fibrosis with confluent masses of fibrotic tissues seen in other pneumoconioses is possible,

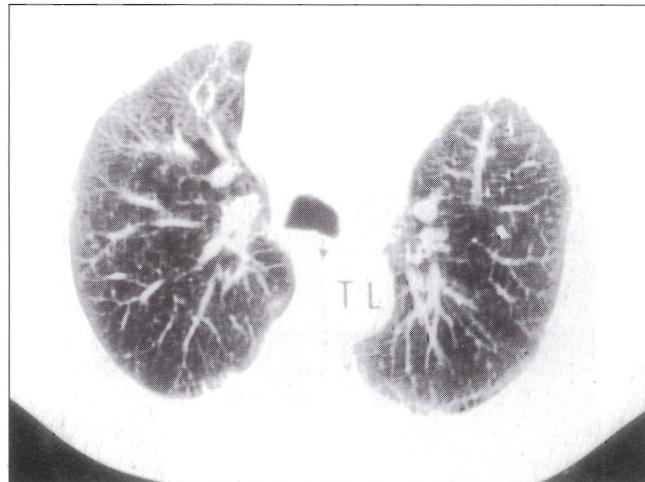


**Figure 6)** Computed tomography scan of an asbestos worker with asbestosis and bilateral minimal pleural thickening. The honeycombing is prominent in both lung fields and parenchymal changes of a reticular nature are well marked

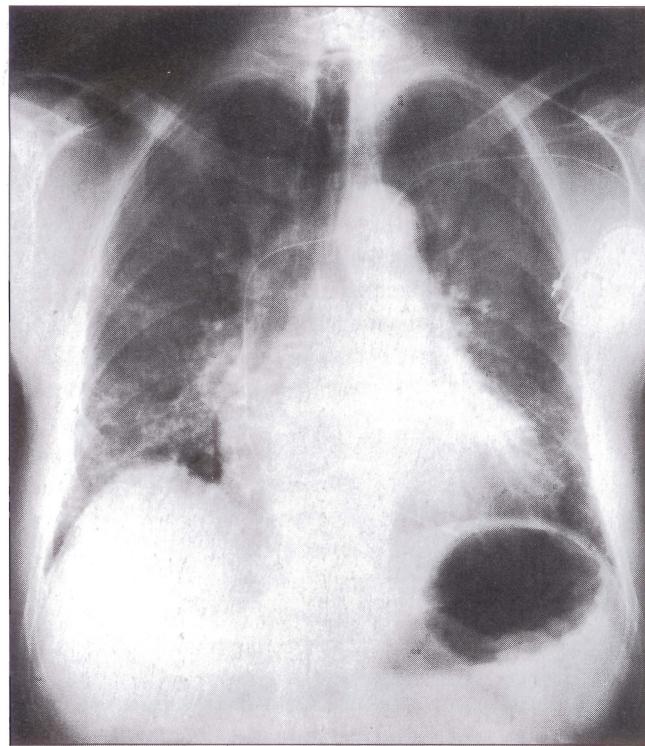
but less frequently seen; a focal mass should be fully investigated for possible tumour.

### Early detection

Pulmonary fibrosis secondary to asbestos dust inhalation is the end-stage of a long inflammatory process. Early in the tissue reaction, one finds macrophage accumulation and activation in the lung periphery, leading to organization of a fibrosing peribronchiolar alveolitis, the fundamental lesion of asbestosis. Later, the process extends into adjacent inter-



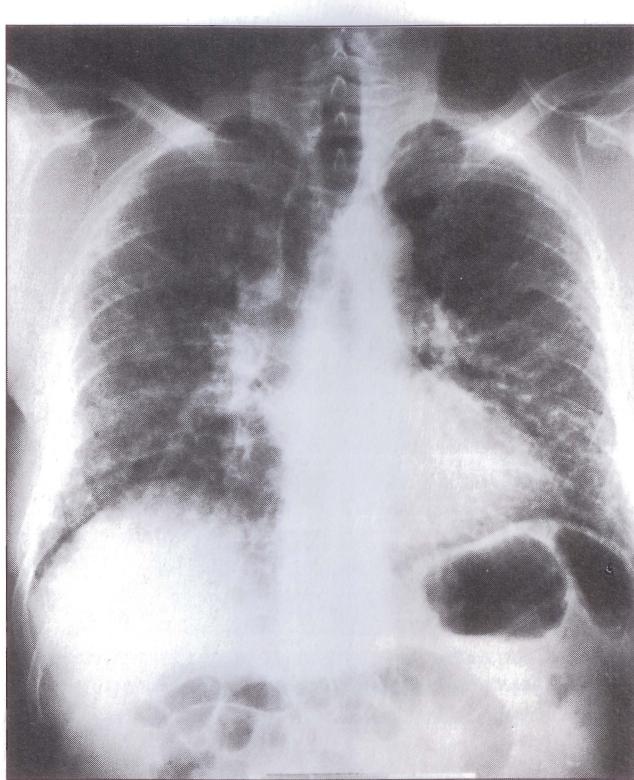
**Figure 7)** Computed tomography scan of an asbestos worker with asbestosis, showing curvilinear lines in nondependent areas, parallel to the pleural surface but located about 1 cm from the subpleural lines



**Figure 8)** Chest radiograph of an asbestos worker showing abnormalities of the lung parenchyma in the lower two-thirds of the lung field as fine increases and thickenings in the vascular markings. There is also a peripheral reticulation of the lung fields, and minimal bilateral pleural thickening. In older patients with cardiomegaly, as in this case, the condition is often confounded with congestive heart failure, at the time of the initial physician visit

stium and progresses to a diffuse fibrosing alveolitis, the lesion recognizable on a standard chest radiograph. To use the various clinical tools appropriately, the clinician must know the sensitivity and specificity of each.

**Crackling rales:** For the occupational medicine physician, the finding of end inspiratory rales in axillary lung fields in



**Figure 9)** **Top** Chest radiograph of an asbestos worker showing more advanced abnormalities of the lung parenchyma. The coarse reticulation is diffuse, of higher density and the cardiac silhouette is beginning to be ill-defined. **Bottom** In an enlarged image of the lower left lung field, the coarse reticulation is better appreciated

an asbestos worker constitutes an early indicator of asbestosis, and correlates well with radiographic findings and lung function changes. In asbestos workers recognized as having asbestosis, rales are usually present. However, in exposed workers not yet recognized as having asbestosis, rales constitute the only abnormality in fewer than 5% of cases (25). Recording rales for further analyses using sophisticated acoustic methods has been of interest but is of limited practical application.

**Chest radiograph:** The standard PA chest radiograph is the main tool in the detection of pneumoconioses. However, it is well documented that in at least 10% of symptomatic subjects

with biopsy-proven interstitial lung disease, the chest radiograph is normal; in asbestos workers, similar observations have been reported. Furthermore, it is not uncommon to find pathological changes of asbestosis in workers not previously recognized on clinical grounds.

**CT scan of the thorax:** Investigation of asbestos workers with conventional 10 mm slice CT scans does not reveal more abnormalities than the standard chest radiograph, but permits a better appreciation of pleural changes. With the newer generation of CT scans and thin 2 mm slices, the clarity and precision have improved significantly and have permitted increased sensitivity. The CT scan with thin slices has now been documented as detecting early interstitial lung disease in 10 to 20% of symptomatic asbestos workers with normal radiographs (39,40).

**<sup>67</sup>Gallium lung scan:** The <sup>67</sup>gallium lung scan has been used for over 20 years to detect occult tumours and infections and more recently to quantify lung inflammation. In the latter conditions, the degree of lung uptake has been correlated with pathological changes. In asbestosis, <sup>67</sup>gallium lung scan detects inflammatory activity as seen pathologically and progresses to radiographically recognized asbestosis in 75% of cases (25,29). It is not a first line method of disease detection but it recognizes the inflammatory activity of early asbestosis, which does not necessarily require withdrawal of the subject from work. The interest in the <sup>67</sup>gallium lung scan has decreased in recent years, largely due to improvement in CT scans.

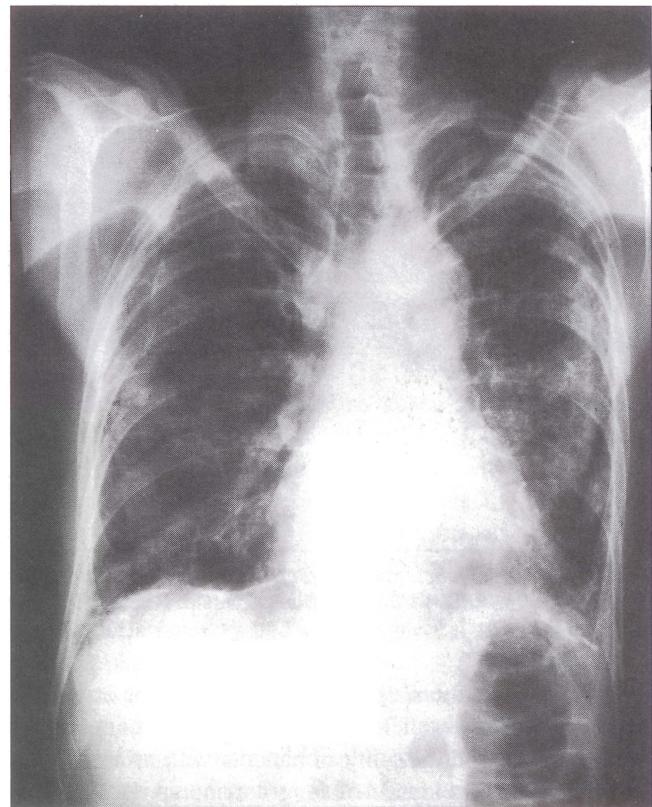
**Bronchoalveolar lavage (BAL):** In the investigation of diffuse interstitial lung diseases, BAL provides new information on the effective cells and biochemical molecules regulating the disease process. In the investigation of workers at risk of asbestosis, BAL is of interest to: eliminate other causes such as silicosis, sarcoidosis, tuberculosis, etc; document the specific mineral dust exposure; support other clinical data suggestive of an alveolitis; and study the biological mechanisms of the disease.

This procedure has shown that some asbestos workers develop a macrophagic and neutrophilic fibrosing alveolitis which precedes the radiographic recognition of asbestosis (16,25).

**Pulmonary function tests:** The abnormalities in the traditional lung function tests such as volumes and diffusion capacity will appear at about the same time as changes in the chest radiograph (25,29,32,41). However, measurement of the lung pressure-volume curve as an early indicator of asbestosis is correlated with changes in the <sup>67</sup>gallium lung scan, BAL and lung biopsies (25,29), demonstrating that these early alterations are associated with peribronchiolar fibrosing alveolitis. Attempts to detect this lesion with the flow-volume forced maximal expiration curve have not been supported by studies in lifetime nonsmokers (29).

### Diagnosis

The criteria for diagnosis of asbestosis have been the object of several task force reports such as that of the American Thoracic Society (42), the Canadian Thoracic Society (43) and other individuals (44). Briefly, most agree that



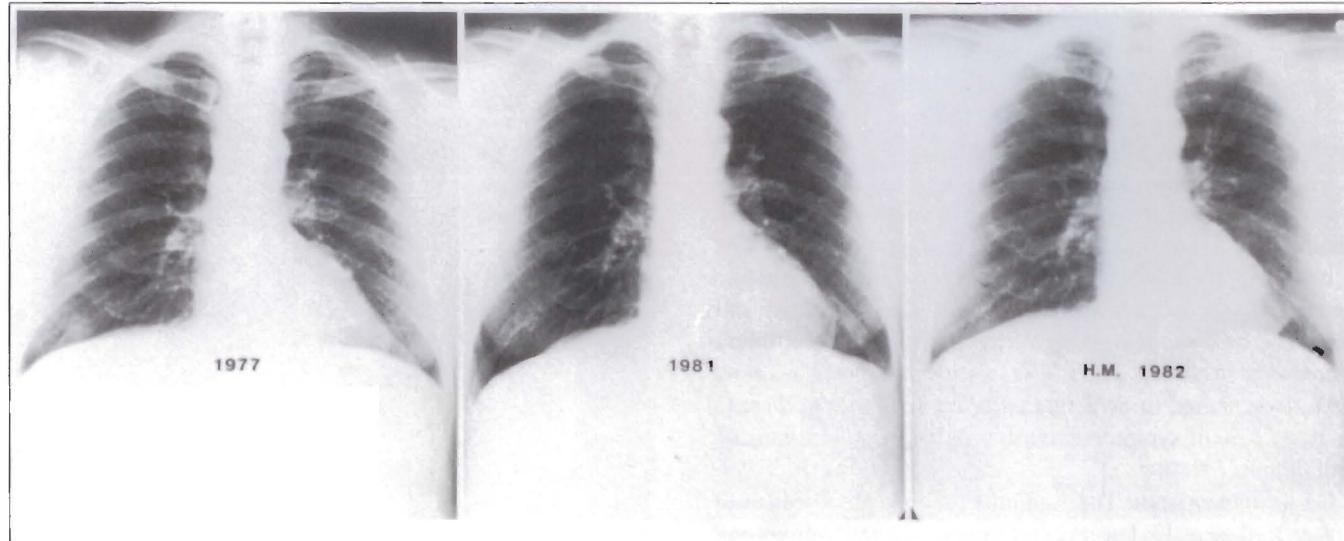
**Figure 10)** Chest radiograph of an asbestos worker showing typical changes of asbestosis, with bilateral interstitial reticular infiltrates and bilateral pleural thickening. This image is almost diagnostic of asbestosis

histopathological material is the most sensitive and specific method, when the pathological examination is coupled with mineralogical assessment. In the absence of pathological material, which is often the clinical situation, the diagnosis of asbestosis is a matter of judgement, based on: first, a reliable and significant history of exposure; second, an appropriate time interval between exposure and detection; third, radiographic evidence of diffuse lung fibrosis, on chest radiograph or CT scan; fourth, a restrictive pattern of lung function impairment; fifth, bilateral inspiratory crackling rales; and sixth, clubbing of fingers and/or toes.

In general, it is suggested that criteria 1 and 3 are essential and the others confirmatory. The extent of the radiological changes needed for the diagnosis of asbestosis is debated, some requiring an International Labour Organization grade of 1/1 and others accepting a grade of 1/0. We are of the opinion that an abnormal chest radiograph or CT scan suggestive of a diffuse interstitial lung disease, in association with a significant history of asbestos exposure, should be sufficient to establish a diagnosis of clinical asbestosis.

### Evolution and complications

The outcome of patients with asbestosis is currently much better than the first cases of Murray (4), who all died before age 30. Although life expectancy after diagnosis of asbestosis



**Figure 11)** Routine chest radiograph from an asymptomatic asbestos miner. **Left** The oldest film, taken in 1977, is normal. **Middle** On the film taken in 1981, left pleural effusion is evident. **Right** On the film taken in 1982, the radiograph is normal again

remains shorter than normal, only 20 to 40% of cases will have a progression of their disease. A significant contributing cause of increased mortality in patients with asbestosis remains the high incidence of lung carcinoma. As in other fibrosing lung diseases, intercurrent bronchopulmonary infections are frequent. There is now experimental evidence to support exposure cessation as a means of reducing the rate of progression (45,46). The deleterious effect of immunosuppressor therapy is well documented in animals and corticosteroid use remains unsuccessful in anecdotal clinical trials. End-stage respiratory insufficiency and failure is still seen occasionally.

### Compensation

Once the diagnosis of asbestosis is established, the worker should not be further exposed to asbestos dust, and compensation for occupational disease should be provided. The modes of compensation vary from one country to another, and in Canada from one province to another.

Whereas for recognition of asbestosis the radiograph has a prominent role, functional impairment is more important in setting of the level of compensation. Asbestosis is progressive and follow-up is required.

### Medical interventions

Medical intervention in cases of asbestosis is important: at the time of initial diagnosis and in the assessment of impairment; to follow progress; in the treatment of intercurrent respiratory infections; and in the treatment of hypoxemia and right heart failure, the late complications of a progressive restriction of lung function. Other modalities of support are prevention of complications and the relief of cough. There is no evidence of benefit from the use of steroids or immunosuppressor therapy in asbestosis, and the latter form of treatment has even been shown to worsen experimental asbestosis.

### BENIGN PLEURISY

#### Pathogenesis and pathology

The pathogenesis of benign asbestos pleurisy is largely unknown (47,48). The clearance of inhaled asbestos fibres is in part through the lung lymphatics, to the interstitium, the pleural cavities and the lymph nodes (49). Direct contact of asbestos fibres with the pleura appears to be the initial event. Recently, an animal model has been developed and the role of chemotactic factors for neutrophils and other inflammatory cells has been stressed (48). The nonspecific inflammatory reaction of benign pleurisy is characterized by an inflammatory reaction with fibrin deposition, accompanied by reaction of mesothelial cells, giving the impression of pseudo-organization (21). This pleurisy is often transient but can leave scars as pleural thickenings in the costophrenic angles, and occasionally result in adhesive fibrothorax.

### Clinical findings

Benign pleurisy is defined by four criteria (50): first, asbestos exposure; second, radiographic or thoracocentesis confirmation of pleural effusion; third, absence of other causes of effusion; and fourth, absence of tumour in a follow-up of at least three years.

This definition is somewhat arbitrary but nonetheless practical. Many workers with benign asbestos pleurisy are asymptomatic and are found at periodic radiography as in the case in Figure 11. Some have shortness of breath and chest pain. The pleural fluid is usually an exudate with or without blood staining. The benign pleurisy of asbestos exposure is asymptomatic in 66% of cases and recurrent in 28% of cases. It is associated with acute chest pain in 17% of cases, with or without fever, and may occur with or without associated asbestosis. According to Epler (50), benign pleurisy is the most frequent abnormality seen in asbestos workers with less than 20 years of exposure. The incidence in the exposed population is in the order of 3%, with a positive dose-re-

sponse relation. It may be seen in white collar workers in the asbestos industries.

Most cases of benign asbestos pleurisy have less than 500 mL of effusion. On physical examination, the findings are those of pleural effusion, with dullness of percussion and pleuritic rub on auscultation. Function measurements show a restrictive pattern proportional to the severity of the effusion and associated pain. The effusion can be transient or recurrent, asymptomatic or symptomatic, uni- or bilateral. The latency period is usually less than 20 years and it is often the first manifestation of asbestos related diseases, but it is not a precursor of other diseases. Usually there is complete resolution of the effusion, but with residual pleural plaques or pachypleuritis.

### Radiology

Pleural effusions are often the first manifestation of malignant pleural or pulmonary neoplasia, and subjects with asbestos exposure and a pleural effusion should be considered as having a tumour until proved otherwise. However, Epler et al (50) have documented that benign pleural effusion is the most frequent disorder seen in the first 20 years following initial asbestos exposure, and usually is the only one to be seen in the first 10 years.

Radiographically, the effusion presents as blunting of costophrenic angles. The fluid is usually of minimal volume, can be mobilized on lateral decubitus films and is transient as opposed to that of malignant tumours. Benign pleurisy can often lead to chronic pleural changes and HRCT can be of help in excluding an early mesothelioma.

### Early detection

This condition is most often asymptomatic and early detection has little interest as prognosis is usually favourable.

### Diagnosis

The four criteria for the diagnosis of benign asbestos pleurisy noted above are somewhat arbitrary but nonetheless practical.

### Evolution and complications

The outcome of benign pleurisy is either toward a spontaneous painless or painful regression with minimal or no pleural scar, one or many recurrences of the effusion and, in a few cases, evolution to diffuse pachypleuritis or rounded atelectasis. It is not a precursor of mesothelioma.

### Compensation

Benign pleurisy is often the cause of temporary work stoppage which should be covered by an insurance plan. Permanent compensation is rarely needed as most cases have only minimal scars, and there is apparently no relationship to other future asbestos diseases.

### Medical interventions

Thoracocentesis and pleural biopsy may be needed to exclude other causes of pleural effusion. Treatment is to relieve symptoms, but follow-up for at least two years is imperative.

## PLEURAL PLAQUES

### Pathogenesis and pathology

The pathogenesis of pleural plaques has been reviewed (47). Two pathogenic theories are suggested: a direct effect of fibres reaching the pleural space and an indirect effect. The latter theory is in part supported by the association of smoking and asbestos pleural plaques. The direct contact theory is more plausible; it recognizes plaques as a local reaction to fibres reaching the pleural space, a preferential way by which short fibres are cleared (49). This latter study has shown that short and thin fibres may be found in the pleural space after inhalation. The thin and pointed nature of the fibres found in the pleural space facilitate penetration into the tissues, with injury and an inflammatory and hemorrhagic reaction organizing to produce pleural plaques. The latter mechanical theory is partly based on the observations of Epler et al (50) in 44 subjects who developed pleural plaques following transient pleural effusions. Churg (21) has described the occasional transformation of a chronic inflammatory and cellular pleural reaction into an acellular plaque.

Pleural plaques are lesions of hyaline fibrosis mainly located in the submesothelial layers of the parietal pleura at the level of the costal margins, diaphragm and paraspinal areas. They can be found in the pericardium and less often elsewhere in the mediastinal pleura. Visceral pleural plaques are less frequently seen but can extend into the interlobar fissures. Microscopically, plaques are composed of layers of virtually acellular collagen, the surface being covered with a thin layer of mesothelial cells. Calcification of dystrophic type is often found in plaques. Although they are typical of asbestos exposure, generally, there are no asbestos bodies or fibres in the plaques.

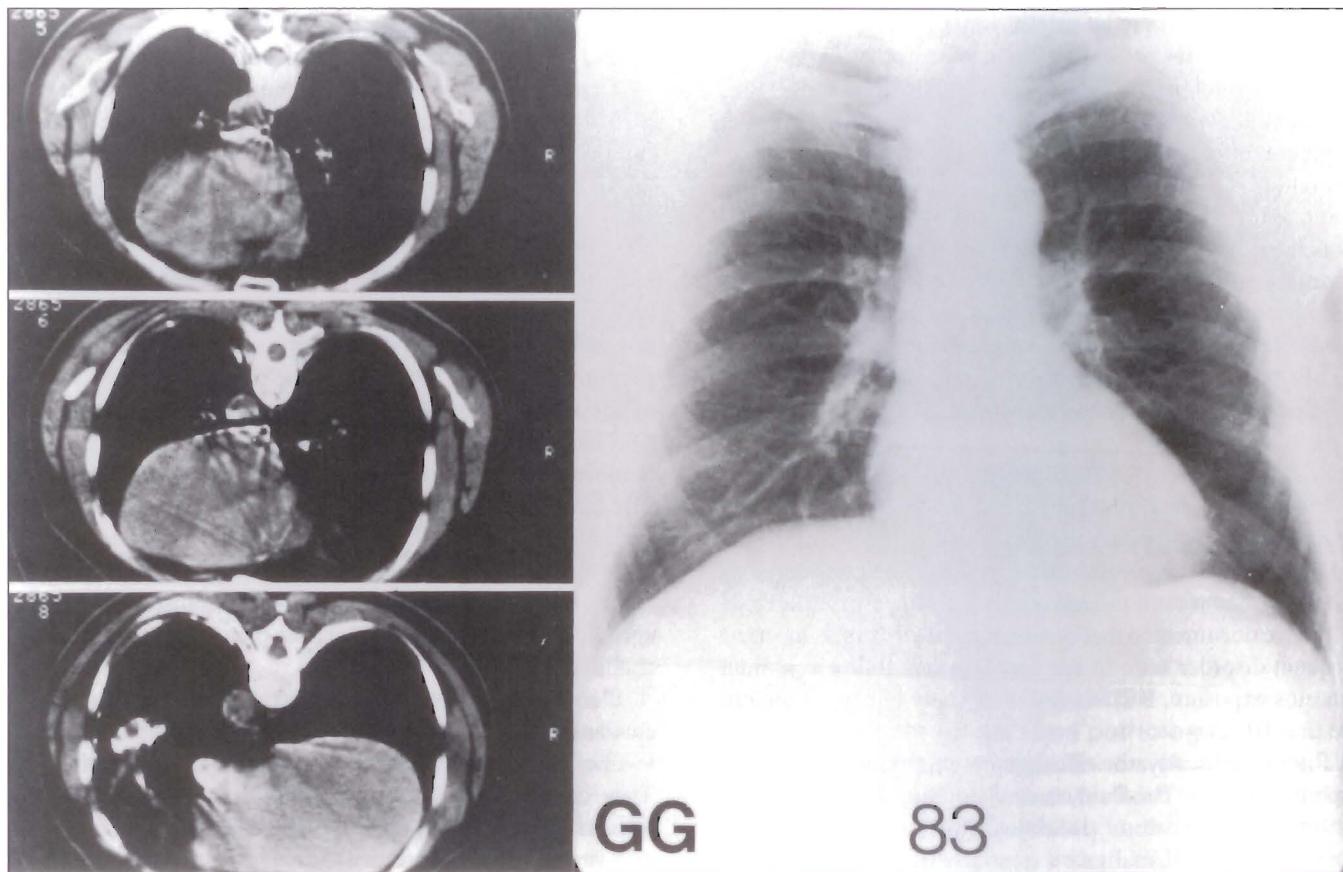
### Clinical findings

Pleural plaques are asymptomatic in the absence of obliteration of the costophrenic angles or associated asbestosis, and have a latency period between initial exposure and radiographic recognition of some 20 years. They have no clinical manifestations, are usually bilateral and often in the retrocardiac area where they are not easily seen on chest radiograph. They have limited progression and are often found in the absence of asbestosis.

### Radiology

Pleural plaques are seen as focal irregular thickenings of the parietal pleura in the submesothelial portion and, in reality, are extrapleural (2,32). They can also be seen adjacent to visceral pleura, uncommonly in the interlobar fissures.

Pleural plaques are the most frequent manifestation of asbestos exposure, and asbestos exposure is the most frequent cause of pleural plaques. Usually, they are considered a good indicator of asbestos exposure, and appear to be related to amphibole exposure; chrysotile has only a limited tendency to produce plaques. Latency time for the production of plaques is on average 30 years with a range of three to 57 years.



**Figure 12)** Computed tomography (CT) scan (left) and chest radiograph (right) of an asbestos worker. The chest film shows normal parenchyma and a calcified diaphragmatic plaque. On the CT scan the diaphragmatic calcified plaque is equally appreciated and, in addition, plaques are also present in the left posterior retrocardiac area, which cannot be seen on the plain chest film

Calcification is not necessarily seen on standard radiographs but affects mainly parietal plaques which are characteristically located along the diaphragm and posterolateral chest wall. They also can be found in paravertebral areas, which are rarely seen on a PA film.

Early, plaques are thin, linear with sharp margins; early detection depends on the thickness of the plaques and optimal radiographic technique. They appear as rounded discrete opacities arising from the parietal pleura, and can have a smooth or uneven surface. Oblique films increase the radiographic visibility of plaques by 50% over the standard PA and lateral chest films. With time, the margins of plaques become more rounded and better defined. Plaques rarely occupy more than four intercostal spaces.

The CT scan can show plaques much earlier and at a less well defined stage than the chest radiograph (Figure 12). The paravertebral and pericardiac plaques particularly are better seen. The diaphragm plaques, which were not always well identified with CT, are correctly evaluated with multiple thin slice HRCT. The CT scan can clearly differentiate plaques from extrapleural fat pads, which may be difficult on the plain chest radiograph. Furthermore, in the presence of extensive and calcified pleural plaques, CT scan permits a clearer appreciation of the lung parenchyma than the plain radiograph.

### Early detection

Recognition of pleural plaques in asbestos workers is mainly of interest as a marker of exposure, as in the majority of cases the pleural plaques do not affect lung function. Nonetheless, several recent studies have shown that the CT scan can permit a better appreciation of pleural changes than the chest radiograph. Pleural plaques usually do not take up  $^{67}\text{gallium}$ .

### Diagnosis

Histopathological material is the most sensitive and specific source of diagnostic evidence of pleural plaques which otherwise can be recognized on chest radiograph or CT scan.

### Evolution and complications

Pleural plaques have a tendency to enlarge and calcify with time, and may also become confluent. It has been suggested that mesothelioma may develop at the edge of such plaques.

### Compensation and medical interventions

Localized pleural plaques are indicators of asbestos exposure and do not affect lung function significantly. Thus, they are usually not compensated for, nor are they an indication for work cessation. However, when multiple pleural plaques produce a restrictive syndrome, compensation and work re-

striction should apply as for asbestosis. Medical interventions are limited to the recognition of the nature and cause of plaques.

## PACHYPLEURITIS

### Pathogenesis and pathology

Whereas plaques mainly occur in parietal pleura, the diffuse pleural thickening of pachypleuritis is a disease of the visceral pleura. The pathogenic mechanisms differentiating pachypleuritis from circumscribed pleural plaques are not defined, but the fundamental irritative mechanism remains likely. In the case of pachypleuritis, fibres deposited in the parenchymal subpleural areas may lead to diffuse pleural fibrosis with associated interstitial lung fibrosis (48). The mechanisms which cause pleural fibrosis to extend into the interlobular spaces of the lung are unknown, but could result from three phenomena: first, the confluence of large pleural plaques in 10 to 20% of cases; second, the extension of subpleural fibrosis to the visceral pleura, resulting in a diffuse pleural thickening in 10 to 30% of cases; and third, the scar of an exudative benign pleurisy producing a diffuse pleural thickening. The latter is the most frequent and often causes significant restriction of lung expansion, even in the absence of interstitial lung fibrosis (48).

### Clinical findings

The diffuse nature of the pachypleuritis is responsible for the symptom of dyspnea on exertion which is often present and relates to significant loss of lung function. Dry cough may also be an accompanying symptom. These diffuse fibrotic thickenings of visceral pleura are not specific to asbestos exposure and can be associated with old inflammatory reactions to tuberculosis, thoracic surgery, hemorrhagic chest trauma or drug reaction. The development of pachypleuritis, contrary to pleural plaques, often follows pleural effusions and is likely initiated by the accumulation of fibres in the subpleural zones of the lung (49). Because of the relative thinness of the fibrosis of the pleura, it cannot be detected easily on physical examination. Diffuse pachypleuritis may be limited to one side or involve both sides and can restrict lung expansion but rarely produces respiratory insufficiency. Most often, asbestos related pachypleuritis is associated with diffuse interstitial fibrosis. In over 30% of cases, there is a past history of asbestos benign pleuritis. Other causes include confluence of pleural plaques in 25% of cases, malignant pleural effusion, chest trauma, pleural infection alone or in combination with one or more of the above (33%), and finally the extension of parenchymal fibrosis to the visceral and parietal pleura (10%).

### Radiology

On the chest radiograph, pachypleuritis is manifested as diffuse pleural thickening with a smooth surface extending over more than 25% of the pleural surface and usually into the costodiaphragmatic angle. Extension of pachypleuritis in two or more fields bilaterally constitutes the best indication that asbestos is the cause.

With a CT scan, pachypleuritis is defined as a pleural thickening more than 5 cm wide, more than 8 cm long and more than 3 mm thick, affecting mainly visceral pleura (Figure 13) in posterior and posterolateral areas of the lower zones. Because of this location, CT scan can provide a better guide to the extent of pleural thickening, compared with chest radiographs. Extension of the fibrosis in the interlobar and interlobular fissures forms a 'crow's foot' appearance or a rounded atelectasis (pseudotumour, with a pleural basis). CT scan is particularly useful in differentiating pleuritis from pleural fat deposits.

### Early detection

Pachypleuritis is not specific for asbestos exposure, and early recognition is of interest mainly because it can alter lung function.

### Diagnosis

Pachypleuritis can be recognized histopathologically and in most cases on the chest radiograph and CT scan.

### Evolution and complications

Asbestos pachypleuritis can restrict lung function extensively if bilateral and severe, and rarely may cause respiratory insufficiency.

### Medical interventions

As pachypleuritis is often due to causes other than asbestos exposure, elimination of the other causes is part of the initial medical assessment, as is the evaluation of functional impairment, which may lead to consideration of compensation for loss of lung function.

## ROUNDED ATELECTASIS

### Pathogenesis and pathology

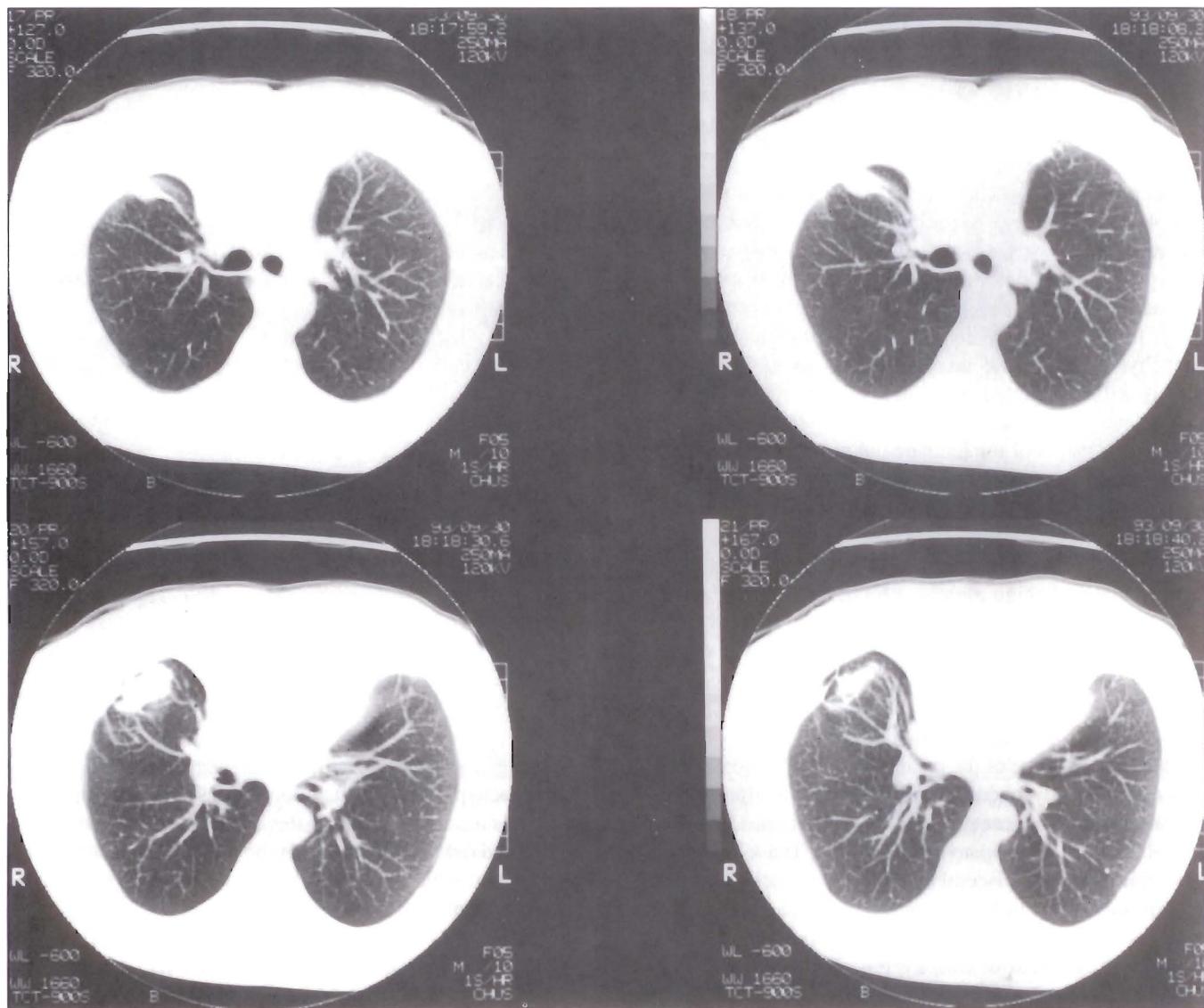
This effect of asbestos-induced pleural disease is caused by scarring of the pleura and adjacent lung tissue, with retraction of the scar tissue and partial collapse of adjacent lung tissue. It is relatively uncommon and the specific mechanisms causing this pleuropulmonary process are not known beyond those causing the pleural disease, but it is more often recognized with the advent of the CT scan.

### Clinical findings

Rounded atelectasis, also called pseudotumour (Figure 13), is usually asymptomatic and is detected on chest radiograph as a pleural based opacity suspected to be tumour in most cases. Occasionally chest pain in the area may be the presenting symptom. In the past, pseudotumours were often resected, but with the CT scan, the true nature of the rounded atelectasis can be recognized without surgery.

### Radiology

Extension of the visceral pleural fibrosis into the interlobar and interlobular fissures is often a late event, seen many years after exposure cessation. It can progress, through retraction of scar tissue, to cause torsion of the adjacent lung



**Figure 13)** Computed tomography (CT) scan of an asbestos worker showing the formation of a pseudotumour in the right lung field. The vascular changes initiated by the rounded atelectasis are seen clearly in the middle window of the CT scan

tissue, giving rise to the rounded atelectasis lesion, folded lung or Bleskovsky's syndrome (Figure 13), also called a pseudotumour, mimicking a carcinoma or confluence of pneumoconiosis. A characteristic feature is a comet's tail rising from the middle of the mass, and may be better appreciated on the oblique chest radiograph or CT scan; it is due to traction of the bronchovascular markings towards the centre of the mass from the hilum.

The diagnosis of rounded atelectasis can be made on the radiological images and usually has the following characteristics: first, round lesion of 2 to 7 cm diameter; second, pleural-based location; third, curvilinear shadows extending towards the hilum (comet's tail); fourth, intrapulmonary location (acute angle between pleura and lesion) with pleural thickening adjacent to the lesion; fifth, thickening of interlobar fissure; sixth, separation of diaphragm from lung tissue; and seventh, slow progression (as opposed to tumours).

### Diagnosis

The diagnosis of rounded atelectasis used to depend on histopathological evidence but the scan has provided images that are quite specific for the condition.

### Evolution and complications

The folded lung is a late manifestation of complicated diffuse pleural thickening. It is slowly progressive and may contribute to restriction in lung function.

### Compensation

Diffuse pleural thickening may cause significant loss of lung function. The criteria for compensation and work restriction should be the same as for asbestosis.

### Medical interventions

Recognition may pose a clinical problem that necessitates the use of CT scan, bronchoscopy and transthoracic needle

aspiration biopsy to eliminate a tumour as the cause of the radiographic opacity.

## LUNG CARCINOMA

### Pathogenesis and pathology

The pathogenesis of asbestos related cancers is incompletely understood and the subject of controversy (1). Some investigators consider asbestos as a tumour promoter as opposed to an initiator, on the basis of weak activity in standard tests for carcinogenic substances (mutagenicity and production of chromosomal abnormalities); the fibres would then have the effect of increasing the susceptibility of the lung to other carcinogens. Others consider the experimental evidence of an excess of lung cancers in animals not exposed to carcinogens other than asbestos, and the excess of lung tumour in lifetime nonsmokers, as being in favour of a tumour initiator. An additional point of debate is the participation of fibrosis in the genesis of lung carcinoma, a position supported by several large epidemiological studies that have found an excess of lung cancers only in the most heavily exposed workers, who also have the highest incidence of radiographic changes suggestive of asbestosis. However, bronchogenic carcinoma is found in lifetime nonsmoking asbestos workers, and these lesions can be produced in animals in the absence of fibrosis.

The existence of asbestos related lung cancers in the absence of asbestosis is further complicated by the smoking risk factor. The 10-fold excess risk of lung cancer in smokers appears to be potentiated to 50-fold in smokers who work with asbestos. The fibre type does not seem to be important, although it has been suggested that crocidolite fibre exposure may represent a high risk. The risk estimate is largely a function of the amount of tobacco smoked and the amount of asbestos exposure. Other risk factors in the workplace, such as contaminant metals, ionizing radiation and other chemicals such as benzopyrene and polycyclic aromatic hydrocarbons, may also contribute to the added risk in the initiation and promotion of lung cancer in asbestos workers.

The pathology of asbestos related cancers is not distinct in type, nature or location within the lung from that associated with cigarette smoking. The cell type distribution is about 35% epidermoid, 25% small (oat) cell, 30% adenocarcinoma and 10% large cell carcinoma. This distribution is not distinct from that of populations not exposed to asbestos.

### Clinical findings

The clinical presentation of asbestos related lung tumours is indistinguishable from that of lung tumours caused by other carcinogens, except for the possible association of symptoms of asbestosis.

### Compensation

In presence of asbestosis, it is universally accepted that lung cancers should be compensated. In the absence of asbestosis, compensation is debatable, some authorities refusing compensation for all cases in the absence of asbestosis, others favouring compensation for cases of long exposure

(about in excess of 20 years), in spite of the absence of asbestosis. A detailed discussion of this point is beyond the scope of this review and the interested reader is referred to Churg (21).

## MALIGNANT MESOTHELIOMA

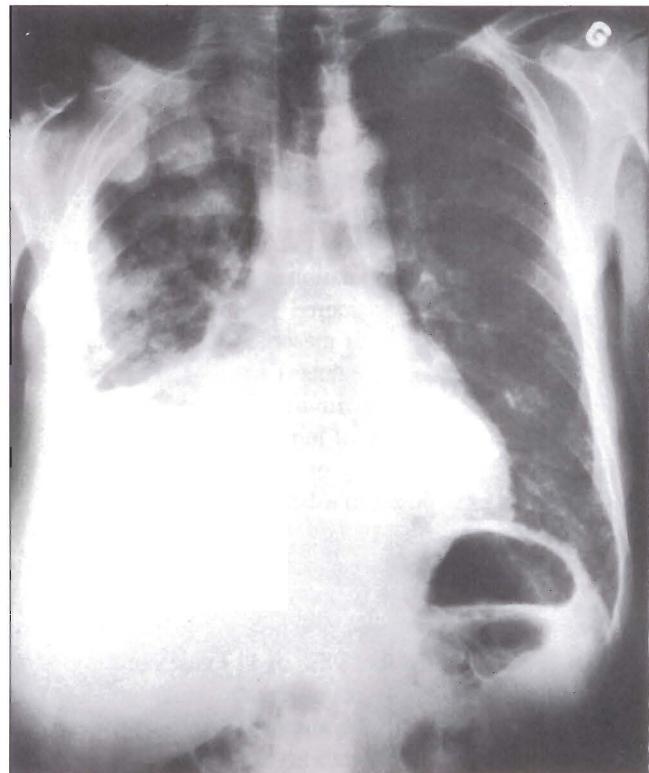
### Pathogenesis and pathology

With an incidence of one to two cases per million people per year in the general population of North America, malignant mesothelioma is considered relatively rare. The clear association of asbestos with mesothelioma was established initially by Wagner and associates (7,13). After the gathering of careful occupational and environmental exposure history and mineralogical analysis of lung tissues, it is overwhelmingly clear that the majority of cases of mesothelioma are found in subjects exposed to asbestos fibres (51-53). Asbestos acts as an initiator and a promoter and thus is considered a complete carcinogen, at least in the induction of mesothelioma in animals. Even in women, in whom the incidence is two to 10 times less common than in men, tissue analysis for mineral fibres revealed that 98% of 117 cases in the United Kingdom had amphibole counts in the lungs greater than controls (54). In general, the amphiboles are considered, in part due to their relative durability, to be the cause of most cases but pure chrysotile cases have also been seen, although to a lesser degree. In some cases, the nearly equal number of the two types of fibres in the lung tissue makes it impossible to establish a causal relationship for either of the fibre types, and all asbestos fibre types have produced mesothelioma.

In animal studies (55) the process starts after fibre injection in the pleura by the formation of a granulomatous lesion with subsequent deposition of acellular dense collagen, which coalesces and is surrounded by a layer of mesenchymal cells and a surface of normal mesothelium. Later, neoplastic transformation with extensive surface growth occurs, showing a variety of differentiation into mesenchymal to epithelial cells.

The rationale for a greater propensity of amphibole to induce mesothelioma in humans has been related to its geometric properties (greater diameter, rigidity), favouring deeper penetration, and its resistance to degradation, favouring its persistence in lung tissues. It is universally accepted that mesothelioma has no association with cigarette smoke exposure.

**Gross pathology:** In the early stages, the mesothelioma appears as multiple small greyish nodules on the visceral and parietal pleura which coalesce and form larger masses of tumour. They are often accompanied by pleural effusion. Tumour will develop by direct extension, forming large masses which invade the adjacent structures, including the chest wall, interlobar fissure, lung parenchyma, mediastinum, pericardium, diaphragm, esophagus, large vessels of the mediastinum, contralateral pleura and the peritoneal cavity. Death is usually caused by restriction of one or more vital structures. Malignant mesothelioma may be of peritoneal origin in fewer than 25% of cases, usually in association with amphibole exposure. The gross appearance of the tumour is

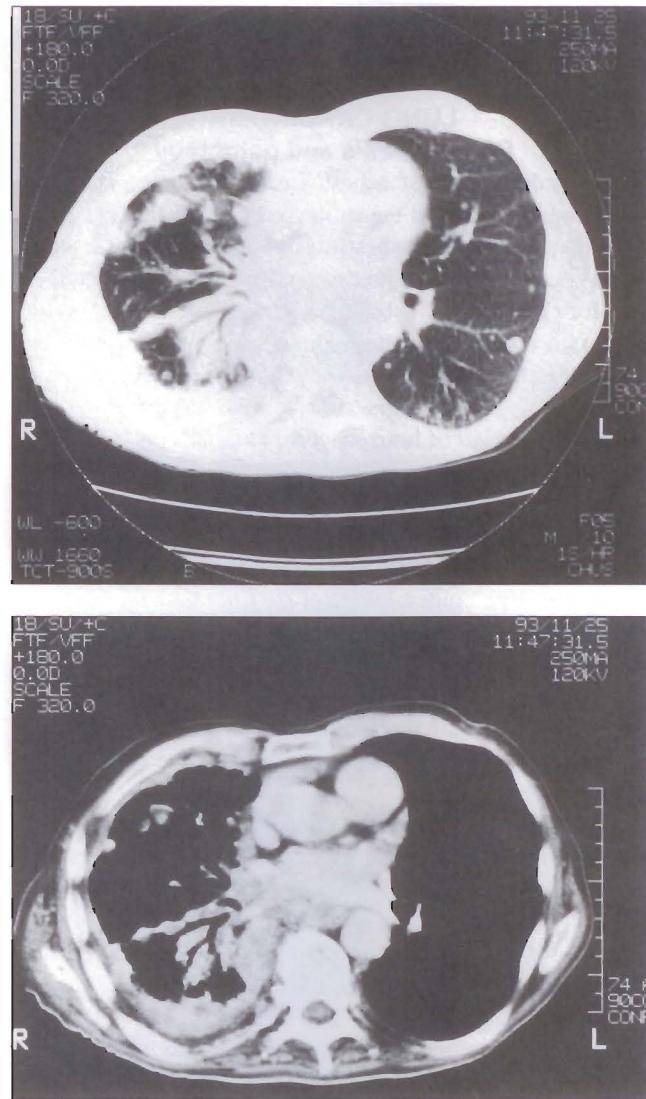


**Figure 14) Above** Chest radiograph in a long term asbestos-exposed plumber. On the chest radiograph the right lung field shows pleural thickening and obliteration of the costodiaphragmatic angle suggestive of pachypleuritis. The reticulation of the left lower lung field on the radiograph is suggestive of asbestosis. In the right lung field of the radiograph, there is a clear obliteration of the costodiaphragmatic angle, some opacities in the parenchyma and some nodularities which, in middle field computed tomography scan (right), are seen to be pleural based and thus highly suggestive of mesothelioma, which was proven on biopsy. On the parenchyma window (top), the nodular nature of the tumour is well seen; a metastatic lesion is also seen in the left lung and on the mediastinal window (bottom) mediastinal invasion can be seen

quite similar to the intrathoracic tumours, and invasion involves primarily the abdominal structures.

**Histopathology:** Malignant mesothelioma has a variety of histological presentations classified as epithelial in some 50% of cases, sarcomatoid in 16% of cases and mixed in 34% of cases. The epithelial type expresses one or more growth patterns such as tubular, papillary, microcystic and solid, which are often mixed within the tumour with some variation from area to area. The sarcomatoid type has spindle-shaped elongated cells; nuclear pleomorphism and mitosis are common. In the mixed form, epithelial and sarcomatous forms are present in variable proportions.

**Histochemistry:** Malignant mesothelioma elaborates acid mucosubstances rich in hyaluronic acid, which can provide a histochemical profile distinct from that of adenocarcinoma, a tumour often considered in the differential diagnosis. Malignant mesotheliomas are usually periodic acid Schiff-diastase (PAS-D) and mucicarmine negative, hyaluronidase-alcian blue positive, whereas adenocarcinomas are PAS-D and mucicarmine positive, but hyaluronidase-alcian blue negative.



The carcinoembryonic antigen is negative in 90% of cases of malignant mesothelioma (and when positive only very weakly) but positive in 90% cases of adenocarcinoma. Cytokeratin immunochemical staining is usually positive and the pattern of staining is distinct from that of adenocarcinoma, being more diffuse in the mesothelioma and exhibiting a predominantly peripheral location in the adenocarcinoma. Vimentin is usually negative in both type of tumours, but may be positive in 20% of mesothelioma cases. The pathological diagnosis of malignant mesothelioma can be very difficult and the expertise of an interested pathologist is often necessary for a final diagnosis.

### Clinical findings

The incidence of malignant mesothelioma is in the order of one per million adults, in the absence of asbestos exposure, and increases to its highest levels in crocidolite-exposed workers. For the general North American population, the incidence rate is estimated at between 2.5 to 13 cases per million adult males per year. In the asbestos exposed popula-

tions, the rates can be five- to 20-fold higher, with a gradient of 10 to 1 for crocidolite to chrysotile exposures (56).

The chief complaint is usually chest pain, dull and aching in nature and occasionally elicited by inspiration, which is persistent and requires progressively higher doses of analgesics. Cough and dyspnea are also frequent, the latter being mainly due to pleural effusion. Weight loss, fever and general malaise are often present. Symptoms of osteoarthropathy are very unusual. Shortness of breath is usually progressive as the tumour extends within the chest to encase the lung and infiltrate the mediastinal structures.

The sites of presentation of mesothelioma can be in the pleural, pericardial or abdominal cavities, the latter being more often seen in cases with high amphibole exposure. The reason for these preferences are unknown.

One of the peculiarities of mesothelioma is the apparent 20 to 50 years of dormancy or latency of the process in humans, which is unexplained but not unique, as other cancers also have a similar dormancy period after exposure; the radiation cancers are an example of this phenomenon.

### Radiology

The radiological findings in malignant mesothelioma are solid pleural abnormalities consisting of diffuse circumscribed thickening with an irregular nodulated surface (Figure 14), multiple pleural nodules or masses of plaque-like opacities and pleural effusion.

As the disease progresses, there may be involvement of the lung parenchyma, reduction in the size of the involved hemithorax, mediastinal and hilar invasion, pericardial thickening and effusion, abdominal extension and chest wall invasion.

Most of these changes can be appreciated on plain chest radiograph but the CT scan adds precision and clarity to the observations.

### Early detection

There is no method of early recognition of mesothelioma at the present time. The majority of patients with mesothelioma have chest pain as the earliest reason for consultation.

### Diagnosis

Open thoracotomy biopsy is usually needed to establish a firm diagnosis of malignant mesothelioma. The combined

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use of microscopy and immunohistochemistry is usually diagnostic.

### Evolution and complications

Diffuse pleural thickening often restricts lung function and may be as limiting as asbestosis.

### Compensation

All malignant mesotheliomas that are associated with a significant asbestos exposure at work should be fully compensated as the disease is nearly always fatal within 24 months of diagnosis.

### Medical interventions

The various therapeutic modalities for malignant mesothelioma include surgery, radiotherapy, chemotherapy and recently immunotherapy or cytokine therapy; all have been equally unsuccessful in curing the disease. At best, an extension of a few months of survival after initial diagnosis may be demonstrated objectively in selected studies (14). Medical interventions remain supportive in nature by providing symptomatic relief.

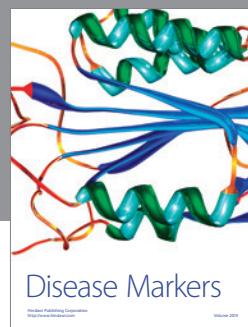
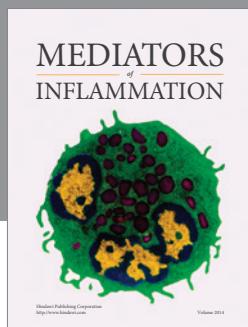
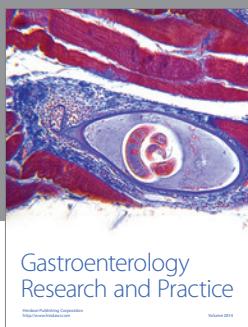
### Prevention

Current practice in public health regarding the protection of workers against the risk associated with their job is legislated in each country. The laws in each Canadian province establish standards of permissible exposure levels and health surveillance of workers by periodical medical examinations. Interested readers are referred to a detailed International Labour Organization publication (57).

### INDUSTRIAL HYGIENE

Industrial hygiene is based on the traditional techniques of reduction in dust exposure by enclosure of the sources of dust, adequate ventilation, coating and sealing of products, the use of specialized tools and frequent cleaning of the workplace. In some particularly dusty circumstances, individual protection is recommended. Hygienists use the threshold limit values for specific dusts as standards to regulate the industrial hygiene conditions. The threshold limit value for asbestos is 1 fibre/cm<sup>3</sup> of air for chrysotile and 0.2 fibre/cm<sup>3</sup> for amphiboles in most industrialized countries.

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