

Emerging Pleuropulmonary Diseases Associated With Asbestos Inhalation

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Introduction

Asbestos is a generic term applied to a group of fibrous minerals found in nature. Because of their particular physical and chemical characteristics, these materials have been used by humans since antiquity. Around 456 BC, Herodotus wrote about the use of asbestos clothing in cremation ceremonies. Plutarch (46-120 BC) described the lamp wicks of the vestal virgins as vegetable fibre mixed with an indestructible material called asbestos.¹

During the nineteenth century, the commercial exploitation of asbestos mines began in Russia, Italy, Canada, and South Africa. Later, with the advent of the Industrial Revolution and the Second World War, demand for asbestos grew and its uses multiplied spectacularly. During this period, asbestos played a decisive role in the development of numerous industrial sectors, and its heat resistant characteristics prevented many deaths. However, soon afterwards its harmful affect on human health began to be noticed. The term “asbestosis” first appeared in print in 1927 in reference to the pulmonary fibrosis caused by the inhalation of asbestos dust,² and in 1935 this illness was associated with the presence of lung cancer.³ In 1960, it was suggested that asbestos was the cause of mesothelioma.⁴ Many studies carried out since then have confirmed the relationship of asbestos exposure with asbestosis, lung cancer, and mesothelioma (Table 1).

In spite of these observations, asbestos use continued to increase. In 1964, the New York Academy of Sciences organized a conference to warn the public about the dangers of exposure to asbestos and to advocate limiting its use, but these initiatives were slowed by pressure from the industrial lobby.^{5,6} By 1980, world asbestos production had reached 5 000 000 tons annually (Figure 1). The subsequent decline in the use of this material has been gradual, and its use was not regulated until many years

later, so that experts estimate that the number of workers in the European Union exposed to asbestos between 1990 and 1993 was around 1 200 000.⁷ It was not until 1982 that the first legislation governing asbestos came into force in Spain. A Ministerial Order of July 31 of that year prohibited the use of asbestos in aerosol form, and subsequent regulations have limited its use and sale (Ministerial Order of January 7, 1987, Royal Decree 1406/1989). In December of the present year European

TABLE 1
Pleuropulmonary Manifestations Associated With Asbestos Exposure

Neoplasias
Pleural mesothelioma
Lung cancer
Pneumoconiosis
Asbestosis
Benign pleural abnormalities
Pleural plaques
Benign pleural effusion
Pleural thickening
Rounded atelectasis

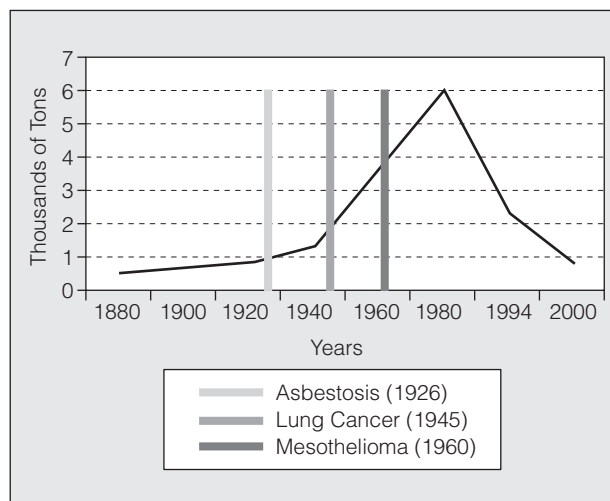


Figure 1. Evolution of world asbestos production and appearance of the diseases caused by asbestos inhalation.

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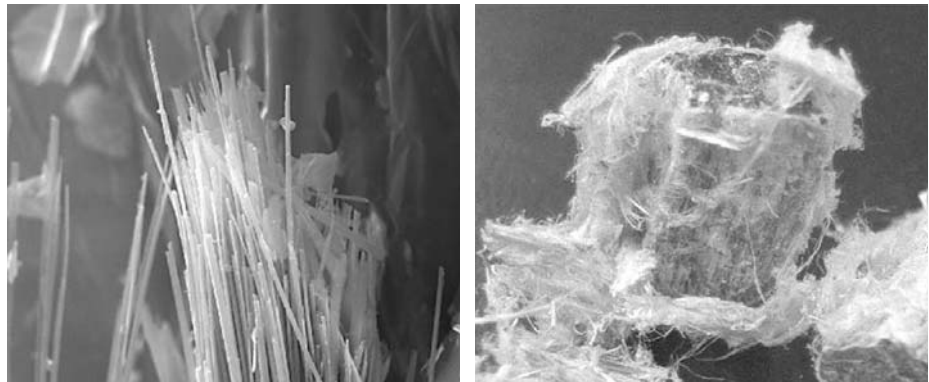


Figure 2. Crocidolite and chrysotile fibers.

Union Directive 1999/77 will come into force prohibiting any use of asbestos in the European Union.

Owing to the delay in adopting these measures of control and the latency period characteristic of this disease, we are currently experiencing a progressive increase in the incidence of lung diseases associated with asbestos exposure.⁸ This is aggravated by the persistence of fibers in our environment in the form of materials present in various manufactured products as well as construction materials that still form part of many buildings. For this reason, even after the total ban on the use of asbestos comes into effect there will still be workers exposed to this product in jobs involving demolition and waste management. In light of these circumstances, a reasonable estimate is that asbestos-related diseases will continue to emerge, and that their incidence will peak during this century, so that this group of clinical entities should be considered a serious and current public health problem of the first order.⁹

Mineralogical Characteristics and Sources of Exposure

Asbestos is the generic name for a group of naturally occurring hydrated silicate minerals possessing fibrous morphology and a crystalline structure. These minerals can be classified into 2 subgroups on the basis of their physical properties and chemical structure. The biological behavior of each type is different (Table 2). Chrysotile is the most commonly used type of asbestos, accounting for approximately 90% of industrial applications (Figure 2).

Some 3000 known applications of asbestos include almost every industrial sector: construction, automobile manufacture, aeronautics, shipbuilding, pharmaceuticals, textiles, railway manufacture, and nuclear power. It is even found in domestic products, such as toys, paints, and smoking accessories. The industrial presentations of asbestos can be classified according to their physical features as follows: *a*) bulk asbestos (used to lag ovens, boilers, and pipes; in doors, refrigerators, vehicles, acoustic insulation, etc.); *b*) sheets or plaques (incorporated into the paper or cardboard used to insulate false ceilings, fire doors, and small electrical appliances, such as toasters and grills); *c*) woven or twisted (fire resistant clothing, insulating tape, jointing); *d*) fibrous cement (flat or corrugated roofing, panels, cladding, chimney flues, water pipes, gas pipes and garden accessories); and *e*) incorporated into binders (resins, bitumen, in automobile brake and clutch linings, trains, plumbing, paint, paving, and vinyl asbestos, among others). The danger of these manufactured products mainly stems from 2 factors: the friability of the fibers they are made of—in other words the ease with which they will fragment or be pulverized and remain suspended in the ambient air—and the state of conservation of the materials that contain them.

When they are not in good condition owing to use, vibration, sanding, or other similar processes, these materials break down and release fibers into the air. In general, the materials not considered to be very friable are asbestos-reinforced PVC (polymers of vinyl and chloride) and plastics, adhesive mastics, adhesives, and paint. Highly friable materials include lagging, spray asbestos, and textiles. Fibrous cement products are considered to

TABLE 2
Characteristics of Asbestos Fibers

Type	Form	Diameter	Length/ Diameter	Acid Resistance	Alkali Resistance	Temperatures Resisted (°C)	Color	Biopersistence	Braiding
Amphiboles									
Crocidolite	Straight	Very small	Very high	Good	Good	900	Blue	Very long (decades)	Acceptable
Amosite	Straight	Small	High	Acceptable	Good	600	Brown	Long	Acceptable
Serpentine									
Chrysotile	Curved	Small	Low	Bad	Good	450	White	Short (months)	Very good

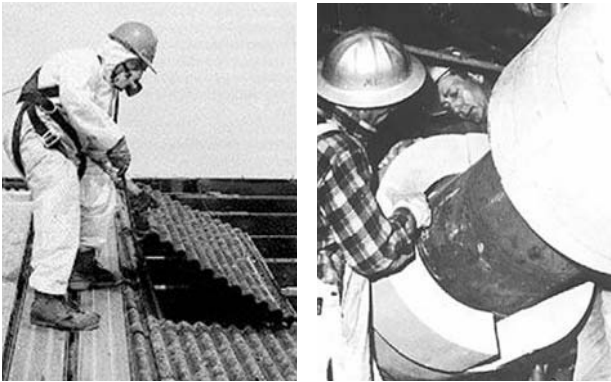


Figure 3. Various industrial applications of asbestos.

occupy an intermediate position in this respect.

The most important source of exposure is occupational (Figure 3).^{10,11} The term paraoccupational exposure refers to the exposure of individuals who spend time in places close to work areas where asbestos is handled and of people who live with exposed workers and are exposed to contaminated work apparel. Ambient exposure occurs in areas located in close proximity to mines and in regions where the subsoil is rich in asbestos (Table 3).¹²

Now that asbestos use has been fully regulated, the activities that currently carry the greatest risk are those related to the demolition and repair of old buildings and industrial plant where the asbestos content is high.

Asbestos Deposition and Clearance

Once released, asbestos fibers remain suspended in the air for a long time thus favoring the persistence of the risk of inhalation. The ability of these fibers to penetrate the respiratory system is variable and depends on their diameter, and to a lesser degree their length, form, and rigidity. Fibers up to 100 μ long are found in the lung parenchyma. Timbrell¹³ showed that the most dangerous fibers are those with a diameter of under 3 μ and a ratio of length to diameter of more than 3:1. The clearance

mechanisms also differ depending on the type of fiber involved. When fibers are very long, macrophages are ineffective, so that long fibers once deposited are rarely eliminated, unless they break (something that occurs quite often with chrysotile but rarely with amphiboles. In general chrysotile has a half life of months, while amphiboles can remain in the lung for decades.^{14,15}

The shortest fibers usually make their way to the alveoli and are eliminated more easily by the lung clearance systems. Although the way the fibers reach the pleura is not entirely understood, they may travel by the pulmonary lymphatic system via intercostal and diaphragmatic vessels.¹⁶ The properties of chrysotile asbestos fibers facilitate their deposition in the pleura, and Sebastien et al¹⁷ have shown that when asbestos fibers are observed in the pleura they are nearly always short chrysotile fibers. Amphiboles, on the other hand, are rarely seen in that location.

The Measurement of Intrapulmonary Asbestos Concentrations

The importance of establishing the occupational origin of pleuropulmonary asbestos-related diseases is obvious in light of the medical and legal repercussions and preventative implications. Although the patient's occupational history is a good tool for identifying exposure,¹⁸ the widespread use of asbestos in varied ways sometimes makes source identification difficult. The observation and quantification of the asbestos fibers in biological samples is a pertinent source of information.

Identification of ferruginous bodies in lung secretions. Ferruginous bodies (FB) are inorganic fibers coated with ferroprotein. Given that in over 95% of cases, the inorganic material present inside the FB is an asbestos fiber,¹⁹⁻²¹ in clinical practice the terms FB and asbestos body are usually considered synonymous. The findings of a qualitative study of FB in respiratory secretions (sputum, bronchial aspirate, or bronchoalveolar lavage [BAL]), reported as the presence or absence of FB, are useful for identifying exposed individuals but not accurate enough to determine whether the asbestos deposits in lung tissue are sufficiently concentrated to cause disease. The sensitivity of FB in sputum or bronchial aspirate is not very high, and the test will only be positive when occupational exposure has been very intense and lung tissue fiber counts are very high. Even when these conditions have been met, the sputum examination will only correctly identify up to 50% of cases with asbestos concentrations in the lung parenchyma capable of causing disease.²²⁻²³

Bronchoscopy is essential for the qualitative study of FB in BAL, but more precise identification of subjects with pulmonary asbestos deposits large enough to cause disease can be achieved with this semi-invasive technique when the qualitative examination is complemented by quantification of the FB in the lavage fluid. In a recent study carried out by Pifarré et al²⁴ on subjects with differing degrees of asbestos exposure, it was determined

TABLE 3
Sources of Asbestos Exposure

Occupational exposure
Construction and demolition
Automobile industry
Shipbuilding
Textile manufacture
Fibrous cement manufacture
Railway sector
Electrical sector
Acoustic and thermal insulation
Waste transport, treatment, and management
Domestic exposure
Fibers on family member's work apparel
Construction components in the home
Domestic consumer products
Environmental exposure
Proximity to asbestos mines
Subsoil rich in asbestos mineral

that the sensitivity of the qualitative examination of BAL for the identification of a clinically significant asbestos deposit in the lung parenchyma fell short of 60%, although the specificity of this measurement was around 90%. Thus, the observation of FB in the qualitative examination of BAL is a useful diagnostic tool in clinical practice, but the absence of FB does not allow us to rule out significant exposure unless FB concentration in the lavage has been quantified. To do so, BAL material must be collected in three 50-mL aliquots of physiological saline solution from the middle lobe or the lingula. Subsequently, a sample of 10 mL or more taken from the second or third aliquot of the BAL should be chemically digested using a 5% solution of prefiltered sodium hypochlorite. The resulting sample must be filtered through a 0.8 μ polycarbonate filter and examined under an optical microscope ($\times 20$ - $\times 40$) to count the number of FB present; the result is expressed as the number of FB per mL of BAL.

FB concentration in BAL correlates closely with the FB content in lung tissue,²⁵⁻²⁷ so that this measurement facilitates accurate identification of individuals in whom the FB content in the parenchyma is high enough to cause pleuropulmonary disease. In 1988, De Vuyst et al^{25,27} found that when a concentration of asbestos bodies of more than 1 FB per mL of fluid was found in BAL, in 85% of cases the concentration detected in lung tissue was over 1000 FB per gram of dry lung tissue; and when over 10 FB per mL was found in BAL, the lung tissue concentration exceeded 10 000 FB per gram. In the same year, Sebastien et al²⁶ found that a concentration of more than 1 asbestos body per mL in BAL predicted a concentration in the lung parenchyma of between 1050 and 3010 asbestos bodies per gram of tissue, so that a count of more than 1 FB per mL in BAL is considered to be associated with an asbestos deposit in the lung parenchyma of over 1000 FB per gram of dry lung tissue,^{25,28-31} a concentration capable of causing mesothelioma or bronchopulmonary neoplasia. Therefore, although the observation of FB in the qualitative examination of a respiratory secretion sample can be useful in identifying the existence of a clinically significant intrapulmonary deposit, it should not be considered sufficient for the diagnostic study of patients suspected of suffering from asbestos-related pleuropulmonary disease.

Identification of FB in the lung tissue. The examination of the FB content in the lung parenchyma is the technique most recommended for the study of asbestos-related diseases when lung tissue is available for study. In this context, measurement of FB concentration in lung tissue is also essential since low concentrations of FB in the lung parenchyma—insufficient to cause disease—have been observed repeatedly in subjects who are exposed to asbestos simply because they live in urban areas, not because they have had contact in the workplace.³²⁻³⁴ In a study carried out in Spain in an urban population not exposed to asbestos, Monsó et al³⁵ observed a maximum

concentration of 500 FB per gram of dry lung tissue in all the cases studied, a much lower concentration than the 1000 FB per gram threshold below which disease does not appear.³¹

Determining the FB concentration in lung tissue requires medium sized lung samples, meaning that transbronchial biopsies are not suitable. Fibers can be counted on surgical or autopsy samples by examining a healthy area of the lung parenchyma situated at a distance from the main lesion—when a lesion (neoplasm) exists—and not immediately subpleural. The samples, which should measure 2 to 4 cm², can be processed fresh or stored in prefiltered formol and are weighed after spending 48 hours at 60 °C before processing in order to determine the dry weight of the tissue. The organic material in the sample is destroyed by chemical digestion using a 5% solution of prefiltered sodium hypochlorite or by incineration and the sample is then filtered through an 0.8 μ polycarbonate filter. The filters are then examined under optical microscope to count the visible FB, and the result is expressed in number of FB per gram of dry lung tissue, dividing the number of FB counted by the dry weight of the sample.

Identification of asbestos fibers in lung tissue. Only 1% of the asbestos fibers in the lung parenchyma are coated with ferroprotein and produce FB²⁹ since this process affects only the long fibers (>10 μ m), and the smaller fragments of fiber are not easily coated.³⁶ This means that there can occasionally be a significant difference between the concentrations of FB and asbestos fibers in lung tissue, primarily when small asbestos fibers predominate. These small fibers can reach high concentrations capable of generating asbestosis in the absence of any FB visible by optic microscopy.³⁷ In these circumstances it may be advisable to determine the concentration of asbestos fibers in lung tissue, particularly in the case of patients with suspected asbestos-related pleuropulmonary disease in whom the measurement of FB in lung tissue does not reveal a concentration capable of causing disease. Using microanalysis techniques it is possible to count the number of fibers present in a biological sample, determine their atomic composition, and identify the fiber type. However all of these techniques require an electron microscope and energy dispersive x-ray analysis—complex technology unavailable in most laboratories,^{30,38} making it necessary to restrict the use of this technique to selected cases. Microanalysis is performed by first digesting or incinerating the lung tissue following the procedure described above for measuring the FB concentration. The fibers are then counted under an electron microscope and the resulting concentration is expressed as fibers per gram of dry lung tissue according to the same formula used to calculate FB concentration. Fiber type is identified by analyzing the dispersive energy of x-rays, a technique that makes it possible to determine the atomic composition of the fiber under observation. A count of over 1 000 000 asbestos fibers of more than 1 μ m long or of over 100 000 fibers of more than 5 μ m long per



Figure 4. Pleural plaques in a posterior site. (Image provided by Dr Calvo of the Instituto Nacional de Silicosis, Spain.)

gram of dry lung tissue is considered to mark high deposition in the lungs with the potential to cause disease.³¹

Alterations in the Respiratory Apparatus Related to Asbestos Exposure

Asbestos fibers retained in the distal portion of the respiratory apparatus can cause cancer and fibrosis in the lung and/or pleura (Table 1). Whether one or the other of these processes develops depends on exogenous factors related to the intensity of the exposure, the characteristics of the mineral inhaled, and to factors relating to particular individuals which may make them especially susceptible.^{39,40}

Non-Malignant Pleural Manifestations

The involvement of the parietal pleura takes the form of pleural plaques. When the disease settles in the visceral pleura it produces a set of abnormalities less specific to asbestos exposure, which include diffuse pleural thickening, benign pleural effusion, rounded atelectasis, obliteration of the costophrenic recess, fibrotic bands, and apical pleural thickening.⁴¹

Pleural plaques. Pleural plaques are the most common manifestation of asbestos exposure.⁴² Although considered to be a good marker of exposure, they are nonetheless nonspecific, being found in conjunction with very variable lung tissue asbestos burdens. Studies of the possible correlation between pleural plaque size and cumulative asbestos exposure have produced differing results.⁴³⁻⁴⁵ The mean latency period is 20 years, and in 80% of cases plaques are bilateral and stable over time. They are caused by a thickening of the parietal pleura, which is composed of an acellular fibrohyaline connective tissue that can be coated with a layer of mesothelial cells. The presence of calcified plaques indicates a long latency period.

Exceptionally these sometimes contain asbestos fibers, which may be coated. From the pathogenic standpoint, plaques are attributed to a lesion inflicted directly by the fibers that are transported by the lymphatic system to the pleural space, where they cause the surface irritation that triggers an inflammatory and fibrotic process. It is probable that these pathogenic events occur on the submesothelial level since no proliferation of mesothelial cells or pleural adhesions have been observed.⁴⁶ On chest radiographs, plaques are observed in the posterolateral portions of the intermediate lung fields, sometimes extending towards the diaphragm. Plaques located on the anterior or posterior chest wall may be confused with parenchymatous alterations, in which case oblique projections may be useful. They rarely occupy more than 4 intercostal spaces. The system for the interpretation of chest radiographs defined in 1980 by the International Labour Office⁴⁷ is not specific enough for the evaluation of pleural plaques.⁴⁸ Computed tomography (CT), and in particular the high resolution technique (HRCT), is the most appropriate method for observing plaques and resolving the differential diagnosis problems posed by pleural and extrathoracic fat and shadows on thoracic muscles (Figure 4).⁴⁹ Silicosis can also cause pleural calcification, but this disease is usually associated with calcification of the hilar nodes.

When circumscribed, the plaques have no significant affect on lung function⁵⁰ and patients are asymptomatic. Multiple plaques can give rise to a restrictive ventilatory defect and may occasionally be accompanied by the early stages of asbestosis, which has not yet become evident on radiography.⁵¹ Although the results of some studies contradict this, no evidence has been found of a relationship between the presence of plaques and the development of lung cancer.⁵² Plaques require no treatment, but the patient should be monitored regularly in order to ensure early detection of other asbestos-related abnormalities that are susceptible to treatment.

Benign pleural effusion. Benign pleural effusion is the earliest sign of asbestos exposure. The usual latency period is 10 to 15 years, although it can occur after 30 years, and a dose-response relationship exists with respect to exposure.⁵³ The incidence of this sign in the exposed population is around 3%, and it has also been reported in cases of indirect or paraoccupational exposure. It may run its course with or without symptoms and tends to persist for months and recur either on the same or the opposite side. It takes the form of an exudation, which may occasionally be hemorrhagic and does not contain asbestos fibers. In 50% of cases the exudate has a high content of mesothelioma cells. Pleural biopsy usually reveals nonspecific pleuritis, and pleuroscopy sometimes reveals plaques on the parietal wall. Diagnosis is obtained by excluding other disease entities, making necessary a pleural biopsy and a long term follow up of at least 2 years without evidence of malignancy. HRCT is useful for excluding mesothelioma, as it will reveal the presence or absence of surface nodularity on the pleura.⁵⁴ The

prognosis is favorable, tending towards improvement. The following sequelae may persist: pleural plaques and, in rare cases, a diffuse pleural thickening or rounded atelectasis, but these events are not related to the development of mesothelioma.

Diffuse pleural thickening. Diffuse pleural thickening occurs after long latency periods and is secondary to short but intense exposure to asbestos. It is the result of a diffuse fibrosis in the visceral pleura, unilateral or bilateral, which manifests itself as a linear pattern along at least a quarter of the length of the thorax in the craniocaudal direction almost always with obliteration of the costodiaphragmatic recess. It may present areas of calcification and usually forms part of a generalized fibrotic process, which frequently infiltrates the underlying lung parenchyma.⁵⁵ It is not unusual to find asbestos bodies or fibers in both structures. CT is particularly useful in distinguishing pleural thickening from other pleural abnormalities.⁵⁴ Diffuse pleural thickening has been attributed to 3 pathogenic mechanisms: confluence of pleural plaques, spread of subpleural fibrosis to the visceral pleura, and benign pleural effusion evolving towards fibrosis. This last is the phenomenon considered the most common.

Diffuse pleural thickening may give rise to a restrictive ventilatory defect and it is less specific to asbestos exposure than pleural plaques are. However, the concomitant presence of pleural plaques or diffuse interstitial fibrosis supports the diagnosis. This condition requires no specific treatment, but periodic monitoring is recommended in order to detect progression of disease and the appearance of other asbestos-related abnormalities.

Rounded atelectasis. Rounded atelectasis is a form of pulmonary collapse affecting the peripheral portion of the lobe that occurs in patients with pleural disease. A part of the lung is trapped between the 2 pleural layers, which, folding in on themselves, cause the atelectasis. They are also called pseudotumors and Bleskovsky's syndrome. On chest radiographs, such pseudotumors are seen as mass-like opacities adjacent to the pleura. CT/HRCT scans reveal their true nature by showing their continuity with the thickened pleura and the loss of volume of the underlying lung, as well as a linear comet tail sign created by the vessels and bronchi that penetrate the mass (Figure 5). The imaging criteria for establishing this diagnosis are: *a)* rounded opacity 2 to 7 cm in diameter; *b)* base located in the pleura; *c)* presence of curvilinear shadows that extend towards the hilum (comet tail sign); *d)* intrapulmonary localization, revealed by a sharp angle between the pleura and the lesion; *e)* thickening of the interlobular incision; and *f)* separation from the diaphragm by pulmonary tissue. In any case, in the context of known exposure to asbestos, the benign nature of the lesion cannot be assured unless there is evidence that it has been stable over a long period of time (for years). In most cases it will be necessary to resort to diagnostic procedures that

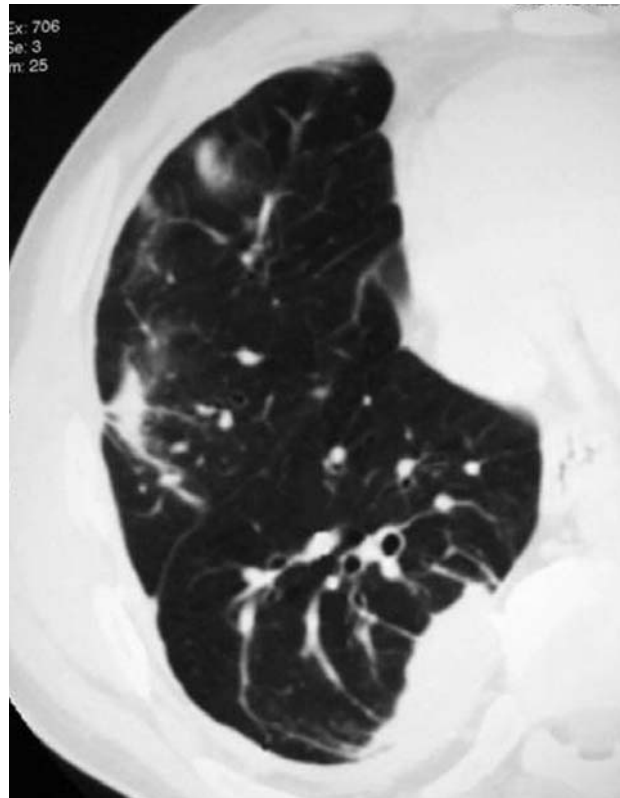


Figure 5. Rounded atelectasis and subpleural curvilinear lines in a chest computed tomography scan.

rule out a malignancy.⁵⁶ Although rounded atelectasis is characteristic of asbestos exposure, it is nonspecific because it is also found in other entities that affect the pleura, such as tuberculosis, trauma, pulmonary infarct, and congestive heart disease.

Lung Disease Caused by Exposure to Asbestos: Asbestosis

The term asbestosis is only used to describe interstitial pulmonary fibrosis in which the presence in the lung tissue of asbestos fibers or bodies can be demonstrated.^{57,58} It is associated with high levels of exposure, and has a latency period of 15 to 25 years. There are no clinical or histopathological findings that differentiate this condition from other forms of interstitial pulmonary fibrosis; only occupational history or the detection of a high burden of asbestos in the lung tissue makes differentiation possible.

The pathogenetic mechanism of this disorder is not completely understood. The process begins when asbestos fibers become impacted in the bifurcations of the respiratory bronchioli and alveoli. These fibers are transported by type I pneumocytes to the interstitial space and cause macrophagic alveolitis. These cells, together with the neutrophils and pulmonary epithelial cells, partially phagocytize the asbestos fibers and a process of cellular apoptosis is induced. The fibers that have not been coated cannot be phagocytized, and chrysotile fibers in particular tend to separate longitudinally, which facilitates

their mobility and interstitial penetration, so that the effects of asbestos exposure persist for a long time after exposure has ended. The alveolar macrophages and epithelial cells that are activated release large quantities of mediators (platelet-derived growth factor, transforming growth factor beta, insulin-like growth factor, and fibronectin), which stimulate the growth of mesenchymal cells. They also release cytokines (interleukin 1 β , tumor necrosis factor, interleukin 8, gamma interferon), oxygen free radicals, and plasminogen activators, locally amplifying the inflammatory response. The oxidizing radicals produce direct cellular toxicity and peroxidation of the lipid components of the cellular membrane; interleukin 8 attracts granulocytes to the inflamed areas; and the platelet-derived growth factor, interferon 1, interleukin 1, tumor necrosis factor, and fibronectin stimulate the proliferation of fibroblasts and collagen biosynthesis, thereby contributing to the tissue fibrosis.^{40,59} Once activated macrophages have accumulated in the peripheral areas of the lung, a fibrosing peribronchiolitis develops and spreads gradually throughout the interstitium, giving rise to fibrosing alveolitis. At this point the process will be visible on the chest radiograph. The American Association of Pathologists has defined 4 stages of increasing severity for this disease, taking into account both the severity and the extension of the lesions.⁶⁰

One of the earliest and most characteristic clinical signs is the presence of inspiratory crackles in the lung bases, although these may be absent in the initial stages. Clubbing occurs in 15% to 20% of cases. Functionally the disease takes the form of a restrictive defect, which may be accompanied by obstruction secondary to small airways disease. Evaluation of the decrease in diffusing capacity is one of the most sensitive methods of detecting the disease in the initial stages, but it has low specificity because such reduction is found in 30% of smokers who have never been exposed to asbestos. BAL usually reveals macrophagic alveolitis accompanied by neutrophilia, and it has been observed that the degree of neutrophilia correlates with the degree of impairment of gas exchange and the likelihood that the disease will progress. BAL is useful in ruling out other disorders, such as sarcoidosis, silicosis, and tuberculosis, among others, and for documenting asbestos exposure. Posteroanterior and lateral chest radiography is the appropriate procedure for initial assessment. Asbestosis is characterized by a pattern of bilateral reticulonodular opacities located predominantly in the lower lung fields, which progresses in the advanced stages of the disease to honeycombing. In the case of low exposures, chest radiography was found to be normal in up to 10% of symptomatic workers in whom the disease had been confirmed histologically. The system devised by the International Labour Office⁴⁷ in 1980 for classifying pneumoconioses was developed for epidemiological purposes, but in practice its use has extended to the assessment of occupational disease, and profusion from grade 1/0 and up is considered to represent an initial phase of the disease. CT and HRCT are more

sensitive techniques; they detect interstitial disease in 10% to 20% of symptomatic subjects with normal plain radiography results and permit better assessment of the associated pleural abnormalities. Their use is, however, only recommended for the assessment of individual cases. Using computed tomography, 5 types of bilateral patterns have been observed to be associated with asbestosis: *a*) curvilinear subpleural lines in the nondependent lung parallel to the pleura but at a distance of 1 cm; *b*) interlobar and interlobular septal thickening in the lung periphery; *c*) nondependent subpleural densities, which are a nonspecific indication of interstitial disease; *d*) parenchymal bands stretching from the pleura to the interior of the pulmonary parenchyma; and *e*) honeycombing with fine wall cysts usually located in posterior zones and nondependent lung areas.^{61,62} When any of these patterns is found in conjunction with pleural plaques, the likelihood that the process is asbestos related increases. Nodal involvement and progressive massive fibrosis are rare unless there has been exposure to silicate.⁶³ Other entities that may present similar radiographic changes include scleroderma, fibrosing alveolitis, and organizing pneumonia.

A firm diagnosis is obtained by histology. This requires evidence of at least 3 discrete foci of fibrosis in the walls of the respiratory bronchioles associated with accumulations of asbestos fibers or bodies. Since the distribution of asbestos fibers or bodies throughout the pulmonary tissue tends to be irregular, a sufficient number of tissue samples should be examined before ruling out their presence. Moreover, since asbestos fibers and bodies are also found in individuals who show no evidence of exposure-related disease, it would also be useful to determine the threshold concentration of asbestos fibers above which the pulmonary fibrosis could be attributed to the presence of such fibers. However, very often no histological study is available, in which case the physician's decision, once alternative hypotheses have been ruled out, will be based on the following: *a*) the existence of a significant documented work history; *b*) a sufficient interval between initial exposure and detection of disease; *c*) abnormalities on radiography indicative of diffuse pulmonary fibrosis; *d*) restrictive ventilatory defect; *e*) persistent bilateral inspiratory crackles; and *f*) clubbing. The first 3 signs are considered essential, the others serve to confirm the diagnosis.⁶⁴ Asbestosis is irreversible and can progress even after exposure has ceased. The course of the disease has undergone marked changes since it was first described at the beginning of the last century. At the outset, asbestosis progressed rapidly, and patients died before they were 30 years old. Today, owing to the industrial hygiene measures applied in most countries and early detection of the disease, most patients diagnosed are over 50 years old and only 20% of them progress to the advanced stages of the disease. In any case, life expectancy is shortened after diagnosis, partly as a result of the high incidence of lung cancer among patients with asbestosis.⁶⁵

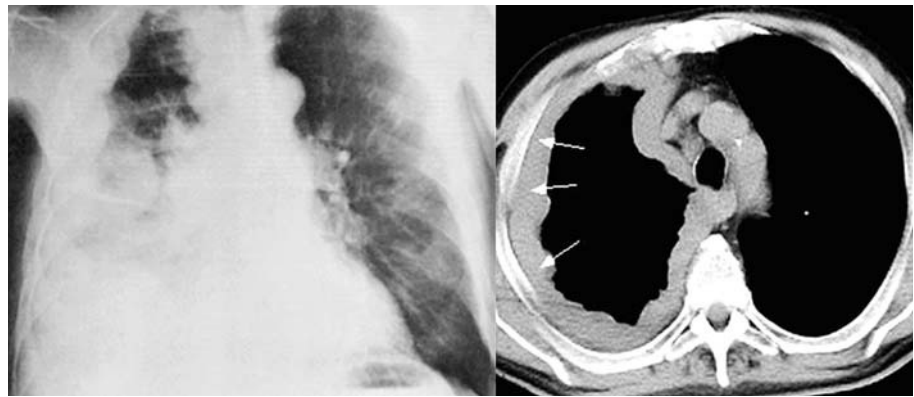


Figure 6. Pleural masses in 2 cases of mesothelioma.

Asbestos-Related Neoplastic Disease

There are no doubts about the carcinogenic effect of asbestos, which derives from its effect on mesothelial cells and the development of malignant mesothelioma. With respect to its effect on bronchial epithelial cells that are exposed to other proven carcinogens, such as tobacco smoke, asbestos appears to act as a co-carcinogen, stimulating the multiplication of previously modified cells.

In any case—even without a complete understanding of its mechanism of action—asbestos has been designated as a group 1 carcinogen by the International Agency for Research on Cancer.⁶⁶

Malignant mesothelioma. This tumor is derived from the mesothelium and can occur in any of the cavities lined by that layer, although the pleura is the most commonly affected. It is a rare tumor with an incidence in the general population of 1 to 2 cases per 1 000 000 inhabitants. Its appearance is not related to smoking, and its association with asbestos exposure is certain. Since it was first described by Wagner et al⁴ in 1960, this association has been confirmed repeatedly by a high level of evidence.⁶⁷ Owing to the long latency period involved—over 30 years—the incidence of mesothelioma is currently growing, and in light of the widespread use of asbestos during the 20-year period from 1960 to 1980, this increase is expected to continue in the future. In the cohorts of workers with the highest exposure—males born between 1940 and 1950—mesothelioma may eventually account for 1% of deaths.⁹ Although this tumor occurs most often in individuals with a history of occupational asbestos exposure,⁶⁸ it has been impossible to find such a history in a certain percentage of cases. In a study of cases and a control group carried out in Spain, Agudo et al⁶⁹ found that 62% of cases of malignant mesothelioma can be attributed to occupational exposure, and they estimate the risk of developing mesothelioma to be 13 times higher among workers with confirmed exposure. It is possible that the group without confirmed exposure had been exposed to unidentified paraoccupational, domestic, or environmental sources.

A clear dose-response relationship has been proved, but it has not been possible to establish a threshold under which no risk exists because there have been cases of mesothelioma attributed to low doses of environmental or domestic exposure.⁷⁰ All types of asbestos can cause mesothelioma, and although crocidolite is associated with a much higher risk, the risk associated with chrysotile, which has been used much more extensively, is also dose dependent.⁷¹ The tumor occurs in the pleura and grows slowly, leading to progressive compression of the lung and invading neighboring structures. The prognosis is very bad, with a survival after diagnosis averaging no more than 2 years. Advanced age, sarcomatous type, and long illness are adverse prognostic factors. Patients with epithelial type tumors survive the longest.^{72,73} The first symptom is usually dyspnea caused by pleural effusion taking the form of an exudate that is difficult to diagnose at the time of presentation. The exudate varies in quantity, is occasionally hemorrhagic, and frequently resolves spontaneously. Another very common symptom is diffuse oppressive chest pain that grows in intensity as the tumor compresses and invades adjacent structures. Involvement of the pericardium can cause symptoms of cardiac tamponade. The findings on physical examination vary depending on how far the disease has spread. The following may be observed: a reduction in size and rigidity on one side of the thorax, a mass in the thoracic wall, malnutrition, and clubbing.⁷⁴ In the initial stages, the most characteristic radiographic finding is pleural effusion, and CT only reveals pleural nodules in less than 10% of cases. Pleural thickening with an irregular surface and multiple nodules or masses may be observed as the disease progresses, and the pleural effusion disappears or loculates (Figure 6). The tumor may sometimes be found in association with pleural plaques or signs of asbestosis. In 50% of autopsies distant metastases are observed in the liver, bones, and suprarenal glands. With respect to histological type, 50% of cases correspond to epithelial tumors, 30% are mesenchymal or mixed, and the rest are sarcomatous. Mesothelioma produces substances rich in hyaluronic acid, which gives it a characteristic histochemical profile, which is useful for distinguishing this entity from adenocarcinoma (Table 4).⁷⁵ Patients suspected of having mesothelioma should be referred to a

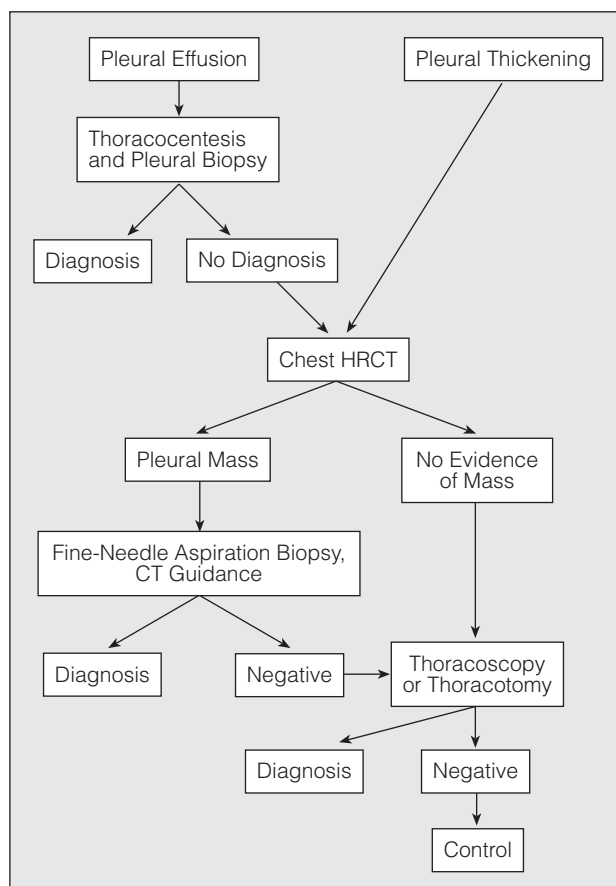


Figure 7. Diagnostic process in suspected mesothelioma. CT indicates computed tomography; HRCT, high resolution CT.

pulmonologist, and the first step should be to investigate the possibility of asbestos exposure, both in the patient's working life as well as any paraoccupational or environmental exposure. The diagnostic process is shown in Figure 7. Pleural biopsy provides a definite diagnosis in only a few cases. In most cases fragments of the tumor obtained by pleuroscopy or minithoracotomy are required. A unique feature of this tumor is that it may spread to the surgical incision, in which case biopsy of the site will provide the diagnosis. Staging the tumor, using the system devised by the International Mesothelioma Interest Group,⁷⁶ is necessary in order to assess the advisability of surgery and polychemotherapy and determine the prognosis. To date, none of the treatments used—chemotherapy, surgery, and radiotherapy—have been shown to modify the survival of these patients to any significant degree.^{77,78} Radiotherapy may be used for

palliative purposes for the control of pain, to reduce palpable masses, and as a prophylaxis to prevent metastases secondary to diagnostic procedures. Radical surgery would only be recommended for epithelial tumors, and should be restricted to hospitals with experience in extrapleural pneumonectomies and associated with chemotherapy. No randomized trials have been published that would allow us to evaluate the increase in survival associated with chemotherapy. The fundamental aims of treatment should be to implement measures for controlling pain and dyspnea using analgesics and pleurodesis if necessary. The most recent lines of research, which include genotherapy,⁷⁹ photodynamic treatment and immunotherapy, have not yet been shown to be useful, although the initial results obtained in preclinical phases seem promising.⁸⁰ With respect to its etiology, mesothelioma may be attributed to asbestos inhalation if certain markers are present, such as the concomitant presence of another related disease or abnormality (asbestosis, pleural plaques) or of asbestos fibers in lung tissue. In the absence of these markers, a history of occupational, paraoccupational, or significant environmental exposure is sufficient, together with a latency period of at least 10 years since first exposure. Patients should be informed of the possible relation between the tumor and work-related asbestos exposure since this circumstance may make them eligible for financial compensation.

Asbestos and lung cancer. An increase in lung cancer in workers exposed to chrome, asbestos, nickel, and radon was observed around the middle of the twentieth century, coinciding with industrial development. In 1935, Lynch and Smith⁸¹ published a first case of lung cancer in a male patient with asbestosis, and called attention to the simultaneous presentation of these 2 conditions. Since then numerous authors have added the following findings: lung cancer appeared in 10% to 20% of autopsies carried out on workers exposed to asbestos, the tumor appeared in younger individuals when they had been exposed to asbestos, and in these workers the tumor was more often located in the lower lobules. On the basis of these findings they sustained that asbestos played a role in the tumorigenesis of lung cancer. Various estimates of the percentage of lung cancer cases attributable to occupational exposure have been published. Simonato et al⁸² reviewed the studies of cases and controls in the literature and set this figure between 8.8% and 40%; moreover, they highlighted the variability of the figure and the high incidence among certain worker populations. Mollo et al⁸³ estimated that in Italy some 2000 cases of

TABLE 4
Differential Immunohistochemical Characteristics

	Mesothelioma	Adenocarcinoma
Cytoplasm	Contains glycogen, not diastase resistant, PAS+	Scant glycogen, diastase resistant, PAS+
Hyaluronic acid	Positive in tumoral cells	Negative in tumoral cells
Positive markers	Nuclear calretinin, cytokeratin 5/6, thrombomodulin	Carcinoembryonic antigen, LeuM ₁ , Ber-Ep4

lung cancer can be attributed to asbestos exposure annually. These figures reflect the magnitude of the problem. In a cross-sectional study carried out in Barcelona, Badorrey et al⁸⁴ attributed lung cancer to asbestos exposure in 4% of cases, and noted the synergistic action of asbestos exposure and smoking.

Furthermore, a dose-response relationship has also been demonstrated. It has been estimated that there is an increase in the relative risk of between 0.5% and 4% for each fiber per centimeter per year (fiber-year) of accumulated exposure. An accumulated exposure of 25 fiber-years would double the risk of cancer. Lung cancer attributed to asbestos inhalation presents the same histology, location, and clinical and radiographic characteristics as cancer due to any other etiology. Consequently, none of these factors can be used to establish cause. Since lung cancer is a disease associated with more than one risk factor,⁸⁶ it is difficult to determine the factor responsible in smokers who have been exposed to asbestos. This is further complicated by the biological interaction that exists between these 2 factors in the genesis of the disease. It is generally accepted that the cancer that appears in a nonsmoker who has been exposed to asbestos is caused by such exposure. The data available would seem to indicate that asbestos exposure always increases the risk of cancer, although to what degree depends on the intensity of the exposure. In workers who smoke the following are used as markers of exposure: the presence of interstitial abnormalities with a profusion score of 1/0 or more on the scale drawn up by the International Labour Office in 1980; signs of asbestosis on a chest radiograph; a history of presumed exposure of more than or equal to 25 fiber-years, and the presence of large quantities of fibers in the lung or in BAL fluid. Pleural plaques occur after low levels of exposure, and therefore they are not valid signs. Diffuse bilateral thickening is associated with moderate to intense levels of exposure. In order to attribute the development of a lung cancer partially or wholly to asbestos, a minimum latency period of 10 years is essential. In studies that have been carried out on the early detection of lung cancer using CT in individuals with pleuropulmonary abnormalities associated with asbestos exposure, the sensitivity of the screening was 100% but the specificity was extremely low.⁸⁷

Prevention, Treatment, and Disability Associated With Asbestos-Related Diseases

Primary prevention is based on industrial hygiene measures aimed at reducing exposure levels by phasing out and removing materials that contain asbestos, isolating its production sources, ensuring adequate ventilation of the work place, protecting and sealing products containing fibers, and implementing special employee protection measures.

Spain now has far-reaching legislation that prohibits and restricts the manufacture, use, and sale of certain kinds of asbestos (amphiboles) and of materials and



Figure 8. Compulsory label for products containing asbestos. Royal Decree 1406/1989.

products that contain this type of asbestos (Royal Decree 1406/1989, which concerns restrictions on the sale and use of certain dangerous substances and preparations; Order of 21 July 1982 of the Ministry of Labour and Social Security on the working conditions of workers who handle asbestos; Royal Decree 1351/1983 of 27 April; Order of 31 October 1984 of the Ministry of Labour and Social Security, which approves the regulations governing work situations associated with asbestos risk; Royal Decree 1406/1989 of 10 November on restrictions on the sale and use of certain substances and dangerous preparations; Order of 30 December 1993 of the Ministry of Labour). Currently the only type of asbestos permitted—with restrictions—is chrysotile. However, the incorporation into Spanish legislation of Community Directive 1999/77/CE prohibiting the use and sale of all kinds of asbestos must be carried out before January 1, 2005.

The limits of work exposure currently in force in most industrialized countries are as follows: 0.6 fibers per mL of air (f/mL) for chrysotile; and 0.3 f/mL for the other types of asbestos.

Three types of intervention are permitted with respect to asbestos already in place: leaving it intact, encapsulation, or removal. Leaving the material untouched is the best option so long as it remains in good condition; it must, however, be adequately labeled (Figure 8) and integrated into an eventual removal program. The removal of in-place asbestos is the most dangerous operation since it provokes the release of fibers to which the workers are exposed. Asbestos abatement comprises a number of different complex operations, and must be carried out by expert operatives. The success of any asbestos abatement operation depends to a large degree the final removal of the material, which is one of the most important phases in this process.⁸⁸ Over the last 20 years,

asbestos has gradually been replaced by other non-asbestos fibrous minerals, such as graphite, carborundum, aluminium oxide fibers, rock wool, fibrous silicates (sepiolite, zeolite, etc.), talc and vermiculite, among others. However, the possibility of some of these materials having pathogenic potential cannot be excluded, and 1 case of pneumoconiosis caused by carborundum and a high risk of lung cancer in animals exposed to ceramic fibers has been documented.⁸⁹

Another prevention measure that must be mentioned is the implementation of antismoking campaigns, which are of particular interest in workers exposed to asbestos fibers. Programs have also been implemented aimed at the chemical prevention of lung cancer through the administration of vitamin A to exposed workers, although the effectiveness of such treatment has not yet been established.⁹⁰

In order to ensure early detection of the possible diseases, exposed workers should be monitored periodically. Such monitoring should be maintained even after workers are no longer exposed. Monitoring basically consist of maintaining a good register of the occupational history of the subjects, a database of information concerning respiratory symptoms and the results of physical examination, posteroanterior chest radiograph, including lateral and oblique projections if necessary, lung function testing, including a study of lung diffusion capacity, and CT or HRCT in selected cases.

There is no treatment for benign pleural disease or for asbestosis, except, in the case of the latter, the appropriate measures that address the patients' functional state and the repercussions of the disease.

Asbestosis is recognized under Spanish legislation as an occupational disease, and the Medical Service for the Prevention of Occupational Hazards (Servicio Médico de Prevención de Riesgos Laborales) is obliged to notify competent authority (the Spanish National Health Service—Instituto Nacional de la Seguridad Social) of all cases that occur. Regardless of the degree of functional impairment, the disease entitles the patient to be declared permanently unable to continue to work in any task involving risk of asbestos exposure. Depending on the severity of functional impairment, the team assessing the worker's case will determine his or her degree of disability and certify entitlement to a life pension, the amount of which varies according to degree of disability (Royal Decree 1995/78, approving the schedule of occupational diseases within the social security system).

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