Guidelines on Asbestos-Related Pleuropulmonary Disease

EROL-SEPAR Work Group
I. Isidro Montes,[a] (coordinator), K. Abu Shams,[b] E. Alday,[c] J.L. Carretero Sastre,[d] J. Ferrer Sancho,[e]
A. Freixa Blanxart,[f] E. Monsó Molas,[g] I. Pascal Martínez,[h] E. Rodríguez Becerra,[i] and F. Rodríguez Panadero[j]

[a]Servicio de Neumología Ocupacional, Instituto Nacional de Silicosis, Hospital Central de Asturias, Oviedo, Asturias, Spain.
[b]Sección de Neumología, Hospital Virgen del Camino, Pamplona, Navarre, Spain.
[c]Servicio de Neumología, Instituto Nacional de Seguridad e Higiene en el Trabajo, Madrid, Spain.
[d]Servicio de Neumología, Hospital Río Ortega, Valladolid, Spain.
[e]Servicio de Neumología, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[f]Laboratorio de Microscopia Óptica y Química General, Centro Nacional de Condiciones de Trabajo, Instituto Nacional de Seguridad
e Higiene en el Trabajo, Barcelona, Spain.
[g]Servicio de Neumología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain.
[h]Sección de Neumología, Hospital Virgen del Camino, Pamplona, Navarre, Spain.
[i]Servicio de Neumología, Hospital Virgen del Rocío, Seville, Spain.
[j]Sección de Endoscopia Respiratoria, Hospital Universitario Virgen del Rocío, Seville, Spain.

Asbestos and some of its properties, such as resistance to heat, has been known to man since 2500 BC, when it was already being used by Finnish potters. The Greeks called it asbestos meaning "inextinguishable," and this is the name still used today in many languages.

The first known patent for asbestos was issued in the United States of America in 1828 covering its use as an insulating material in steam engines. The first asbestos textile factory started production in 1896. After this date, and throughout the twentieth century, a host of applications for asbestos came into general use, and today there are over 3000 known applications.

In view of the repercussions of asbestos use on health and its role in the etiology of respiratory disease, the Scientific Committee of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) asked the society's Work Group on Occupational Respiratory Diseases (EROL) to draw up recommendations in order to provide pulmonologists with clear, concise, and up-to-date guidelines on asbestos-related diseases and their diagnosis.

It has been a great pleasure for me to coordinate this group of Spanish professionals whose demonstrated competence and knowledge of asbestos-related disease is well known.

Introduction

The respiratory diseases caused by asbestos inhalation are many and varied. The first well-documented case of asbestosis (pulmonary fibrosis caused by asbestos exposure) was reported by Dr. H. Montague Murray in the United Kingdom in 1906. The patient worked in the carding room of a textile factory and was the last

Correspondence: Dr. I. Isidro Montes.
Instituto Nacional de Silicosis.
Celestino Villamil, s/n. 33006 Oviedo. Asturias. España.
E-mail: isabel.isidro@sespa.princast.es

survivor of 11 workers who had started together in this workshop. By 1930, over 75 cases of asbestosis had been reported in the scientific literature, and the first cross-sectional epidemiological study had been published in the United Kingdom.

The first indication that asbestos could be a human carcinogen emerged in 1935, and this suspicion was confirmed in 1947 by Dr. E. R. A. Merewether. In 1955, Richard Doll published the first detailed longitudinal epidemiological study of 113 asbestos textile industry workers, who were observed over a 20-year period. There were 11 deaths from lung cancer in this group whereas the expected mortality from this disease in England and Wales at the time would have been 1 case in a group of this size.

Although Dr. Hubert Wyers already suspected the existence of an association between asbestos exposure and mesothelioma of the pleura and peritoneum in 1946, no conclusive evidence was available until 1960 when Dr. Christopher Wagner and colleagues published a study of 33 cases of pleural mesothelioma in a mining area of South Africa where there was exposure to crocidolite.

In Spain, asbestosis and asbestos-related cancer of the lung and pleura figure in the list of occupational diseases specified by Royal Decree 1995/1978 dated May 12.

Epidemiology

Classification of Asbestos Types

The term asbestos (meaning inextinguishable or indestructible) is used to refer to a group of fibrous minerals with differing chemical compositions and structures. Although asbestos has been used since ancient times, it was not until the nineteenth century

that it was first used in industry. Thereafter asbestos use increased continuously until recent decades, when it peaked and started to decline after the high pathogenicity of this mineral was confirmed.

Asbestos minerals are classified into the following 2 groups according to their structure: serpentines (with curly fibers), principally chrysotile or white asbestos; and amphiboles (straight fibers), which include amosite or brown asbestos, crocidolite or blue asbestos, anthophyllite or yellow asbestos, tremolite, and actinolite.

The type of asbestos most commonly used in industry is chrysotile (95% of production); this is followed by crocidolite and amosite and, at a great distance, the other types.

Properties of Asbestos Minerals

Asbestoses are iron, sodium, magnesium, and calcium silicates with a crystalline structure. These minerals are composed of very fine fibrous elements that make up the visible fibers (particles that are >5 μm long, <3 μm wide, and have a length-to-width ratio of 3 to 1 or greater).[1] They have a specific gravity of approximately 2.5 and a melting point of over 1000°C. Owing to their chemical composition, these minerals are heat resistant and can withstand temperatures of up to 800°C. They are resistant to bases (chrysotile) and acids (particularly amosite and crocidolite), this latter property making them useful as insulation materials in industry. Chrysotile fibers are flexible, which makes them suitable for use in the textile industry, while amphibole fibers are more brittle. Owing to the fact that they are incombustible and insoluble, have high electrical resistance, and are highly resistant to wear, asbestos materials are considered to be indestructible. For all the same reasons, asbestos fibers are biopersistent and remain in the lung tissue for a long time. This is what makes them pathogenic.

Pathogenesis

Once inhaled, asbestos fibers travel through the airways, and those not cleared by the mucociliary system move into the alveoli, where they may be engulfed by macrophage cells, eliminated via the lymph system, or may produce fibrosing or carcinogenic effects. The different physical and chemical properties of the different types of asbestos fibers determine their pathogenic risk. Since, the toxicity of the material derives from its fibrous structure, pulverized asbestos does not cause disease. The intensity and duration of exposure are important factors in determining the risk of disease.[2] Researchers are trying to establish an occupational threshold under which there is no risk. Labor laws regulate the length of the working day and the concentration of airborne asbestos dust permitted in the working environment.

The pathogenicity of asbestos fibers appears to depend on their length, aerodynamic breadth, and on the time the fiber remains in the tissue. Fibers with a larger diameter are deposited in the nose, trachea, and large airways, and are eliminated by the mucociliary system. The fibers with a smaller diameter reach the respiratory bronchioles. Experimental studies in animals have shown that short fibers (<5 μm) are less biologically active than longer fibers. The long fibers that reach the alveoli are considered to be more pathogenic because of their slower clearance. Some studies also suggest that the surface properties of such fibers influence the process by acting on the cellular metabolism.[3] Owing to their structure, the long curly chrysotile fibers are more easily retained in the proximal bronchi by the mucociliary system, while the short rigid amphibole fibers penetrate into the bronchoalveolar spaces.

Some authors maintain that the pathogenicity of asbestos fibers is also influenced by host-dependent factors, such as adequate mucociliary activity to eliminate the inhaled fibers and the host's immunological state. The inflammatory response to asbestos fibers appears to be more intense in animals with altered immune status than in controls.

Studies in animals and humans have demonstrated that the macrophages activated by asbestos secrete proinflammatory and profibrotic cytokines, such as fibroblast growth factor, interleukin 1β and 6, tumor necrosis factor alpha, granulocyte macrophage colony stimulating factor, neutrophil chemotactic factor, fibronectin, platelet derived growth factor, and type 1 growth factor, as well as inflammatory mediators, such as leukotriene B4 and the E2 prostaglandins, which play an important role as mediators of the disease.[4-7]

Studies undertaken in recent years point towards a higher risk of lung cancer when the person exposed to asbestos fibers is a smoker.[8,9]

With respect to the importance of the individual's immune system, rheumatoid factor and antinuclear antibodies have been identified in 25% to 30% of exposed workers with normal chest radiographs, but in quantities lower than those usually seen in collagen diseases. However, not all investigators are in agreement on this point.[10] On the other hand, a DNA virus called simian virus 40 is considered to be oncogenic in mesotheliomas, and some authors defend the theory that this virus may act in synergy with the asbestos fibers to potentiate their carcinogenic effect.[11-13]

Sources of Exposure and Uses

There are 3 types of asbestos exposure: occupational, domestic, and environmental. Domestic exposure can be the result of a contaminating source in the home or of family members' exposure to fibers transported in an asbestos worker's apparel. Environmental exposure mainly occurs in countries where asbestos is mined, such as South Africa, Australia, and Canada, where a dusting of asbestos fibers has been detected in an area of some kilometers around the mines and the incidence of lung cancer and mesothelioma is much higher than predicted. Likewise, in countries where the subsoil is

rich in asbestos minerals, such as Turkey (erionite), Corcega, and Cyprus (tremolite), the incidence of mesothelioma is also much higher than predicted.

Occupational exposure occurs in the workplace. At one time, most asbestos was used in the manufacture of asbestos cement products used to make tiles, sheeting, and pressure pipes, as thermal insulation for boilers and pipes, as fireproofing to protect the walls and beams of structures, and to improve the fire resistance of cellulose and other materials. The Spanish Ministerial Order of October 31, 1984 includes the following activities in its area of application: *a)* flue construction when an asbestos material is used; *b)* shipyards, ship breaking, and salvage operations; *c)* extraction, preparation, and transport of asbestos; *d)* manufacture of float filters; *e)* asbestos insulation industries; *f)* asbestos cardboard industries; *g)* asbestos textiles industries; *h)* asbestos cement industries; *i)* demolition operations when asbestos is present; *j)* manufacture and repair of clutch disks and brake linings; *k)* lagging of pipes and boilers; *l)* industrial dry cleaners and laundries; *m)* transport, handling, and destruction of waste material containing asbestos; and *n)* all other operations and activities involving asbestos or asbestos-containing materials whenever there is a risk that asbestos fibers may be released into the work environment.

The Spanish Ministerial Order of January 7, 1987 includes in its area of application: *a)* demolition work if there is any risk that asbestos may be present; *b)* all work and operations undertaken to remove asbestos or asbestos-containing materials from buildings, structures, machines, and installations; *c)* scrapping of ships or other items containing asbestos; and *d)* maintenance and repair work on buildings, installations, and units when there is a risk that asbestos fibers may be released.

Crocidolite, the use of which has been prohibited in Spain since 1987, was used in the manufacture of pressure pipes, as a fireproof insulation in construction, and, because of its high tensile strength, to reinforce plastics.

Today, the workers considered to be most at risk for asbestos exposure are people involved in asbestos abatement operations and those who unexpectedly encounter asbestos in the course of their work, in particular in the maintenance and repair of buildings, factories, ships, and trains. Construction workers will probably be the most exposed group in the coming years because for decades asbestos was used widely in the construction industry and had many applications (Table 1).

Incidence

Determining the incidence or prevalence of asbestos-related disease in the world is an impossible task, and many authors have published different estimates.

The prevalence of radiologically documented asbestosis varies considerably in studies of groups of workers and, as might be expected, this inconsistency in the data is related to differences in the duration and intensity of exposure rather than to differences between workplaces. However, even when these factors are taken into account, restricting the comparison of exposure-response relationships to studies in which exposure was calculated individually for each member of the cohort on the basis of work history and industrial hygiene measurements, considerable differences are observed related to both the fiber type and the industrial process.[14-16] For example, there was a 5% prevalence of small patchy opacities—of profusion 1/0 or more by the International Labor Organization (ILO) classification—as a result of accumulated exposure to approximately 1000 fiber-years among chrysotile miners in Quebec, to approximately 400 fiber-years in chrysotile miners in Corcega, and to fewer than 10 fiber-years in crocidolite miners in South Africa and Australia. Conversely, among textile miners exposed to chrysotile in Quebec, there was a prevalence of 5% of small patchy opacities after an accumulated exposure to fewer than 20 fiber-years.

Studies of fiber lung burden also confirm the existence of differences in the size of the fiber burden required to induce asbestosis.[17,18] While fiber size distribution contributes to these differences, it does not entirely explain them, and this points to the possible influence of other factors specific to each factory, such as other pollutants present in the workplace.[19]

Cohort studies confirm that the risk of lung cancer increases with exposure, although the fractional rate of increase per fiber per millimeter per year of exposure is variable and is related to the fiber type and to the industrial process (Health Effects Institute-Asbestos Research 1991).[20] Cohort studies of asbestos workers also confirm that the cancer risk can be demonstrated in nonsmokers and that it increases (at a rate of progression more multiplicative than additive) with tobacco consumption.[21] The relative risk of lung cancer decreases once exposure ceases, although the decline appears to be slower than that which occurs after a smoker stops smoking. Studies on fiber burden in the

TABLE 1
Uses and Applications of Asbestos in the Construction Industry

Uses	Applications
Woven	Lagging for pipes
Pure fibers	Insulation in air chambers, roofs, and fire doors
Fibrous cement high pressure pipes	Water piping
Acoustic panels	Acoustic insulation
Corrugated fibrous cement panels	Roofing
Low density cardboard or panels	Fireproofing inside metallic structures and false ceiling panels
Bulk asbestos	Fill for air chambers, flocking and coating on surfaces
Asbestos mixed into binders	Graphite, resins, bitumen, metals, plastics, paints, putty, sealers, etc

lung also support the thesis that there is a dose-response relationship between fiber exposure and lung cancer.[18]

With respect to mesothelioma, in the 15 years after the report published in 1960 on the series of mesotheliomas discovered in the north west Cape Province (South Africa),[22] the association between asbestos and mesothelioma was confirmed by reports of other case series in Europe (United Kingdom, France, Germany, Netherlands), United States of America (Illinois, Pennsylvania, and New Jersey), and Australia, and of studies of cases and controls in the United Kingdom (4 cities), Europe (Italy, Sweden, Netherlands), United States of America, and Canada.[23-27] The odds ratio ranged from 2 to 9 in these studies. The association with shipyard work was particularly high in Europe. Moreover, studies of proportional mortality in cohorts exposed to asbestos indicated that the risk was associated with the type of fiber and the industrial process, and that the death rates attributable to mesothelioma ranged from 0.3% in chrysotile mines to 1% in chrysotile factories, as compared to 3.4% in amphibole mines and factories, and up to 8.6% for exposure to mixed fibers in insulation materials.[28,29]

Differences between the sexes in mesothelioma incidence and trends over time have been used to measure the health impact of asbestos exposure on different populations. The best estimates for global incidence in industrialized countries before 1950 are under 1 per 1 000 000 for women and men. After this date, the incidence rises uniformly in men but not in women, at least not to the same extent. This increasing incidence among men probably reflects occupational exposure. If this is the case, incidence should stabilize or fall within the "incubation" period of 20 to 30 years after the introduction of workplace controls and the reduction of occupational exposure levels in most industrialized countries in the 1970s. In the countries where the incidence is rising among women, the increase could be due to the greater participation of women in occupations where there is risk of exposure, or to an increase in environmental or domestic pollution in urban areas.

Asbestosis is more prevalent than bronchial or lung cancer. This is shown in Table 2, which lists information sourced from the Social Security Department of the Spanish Ministry of Labor concerning asbestos-related occupational diseases reported by administrative bodies and other institutions collaborating with the Social Security Department in this matter. The data obtained by the registry set up by the Work Group on Occupational Respiratory Diseases of the Spanish Society of Pulmonology and Thoracic Surgery since its inception are shown in Table 3.

Diagnostic Methods

Work History Associated With Risk

It is essential to record the patient's complete work history and not just the work history involving asbestos exposure since patients are very often unaware of the pollutants to which they have been exposed and are ignorant of the risks involved. This record should start with the first job held by the patient, the time spent in each category, and his or her exposure.

If it is known that the patient has been exposed to asbestos, the following questions should be asked:

– The date of first exposure to asbestos.

– The type of exposure: occupational (working directly with asbestos) or paraoccupational (working beside or in the same space as the worker with occupational exposure).

– The type of asbestos involved in the exposure, if the patient knows (chrysotile, crocidolite, amosite, etc).

– The duration of exposure in years.

– The intensity of the exposure (for example, 8 hours a day or 2 hours a week).

– The latency period (the time that has elapsed since first exposure).

– The level of exposure. The Spanish Ministerial Order of October 31, 1984 deems a worker to have been potentially exposed when the concentration of asbestos fibers, measured or calculated in relation to a reference period of 8 hours a day and 40 hours a week, is 0.25 fibers/cm^3 or greater, or when the accumulated dose measured or calculated over a continuous period of 3 months is 15 fiber-days/cm^3 or more. The problem is that this information will only be available on rare occasions because dust levels in the workplace were not measured before 1987. Owing to the long latency period, the disease we are currently seeing has very often been caused by exposure that occurred before such levels were monitored. Moreover, certain sectors, such as the construction industry, were subjected to a high level of exposure for years without this being known or measured.

TABLE 2
Reported Asbestos-Related Occupational Disease Cases (Spanish Ministry of Labor)

	2000	2001	2002
Asbestosis	17	29	17
Bronchial or lung cancer	5	3	12
Total	22	32	29

TABLE 3
Cases of Asbestos-Related Respiratory Diseases in the SEPAR-EROL Registry of Occupational Respiratory Diseases: Asturias, Catalonia, and Navarre*

	2002	2003	Total
Asbestosis	39	30	69
Mesothelioma	25	15	40
Benign pleural diseases	155	63	218
Bronchial or lung cancer	7	7	14
Total	226	115	341

*SEPAR-EROL indicates the Work Group on Occupational Respiratory Diseases (EROL) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).

Diagnosis Using Imaging Techniques

In standard posteroanterior and lateral chest radiographs, small patchy opacities can be seen, particularly in the lower lung fields. Initially there is a fine reticular pattern, which progresses to a marked linear pattern and eventually to honeycombing in the advanced stages. The different types of patchy opacities are designated by the letters *s*, *t*, and *u*, and profusion is graded between 1/1 and 3/3 according to the ILO scale.[30] In all stages of the disease, the abnormalities predominantly affect the subpleural regions of the lower pulmonary fields. According to the American Thoracic Society, a finding of such signs in conjunction with a work history that is consistent with a diagnosis of asbestosis provides sufficient evidence to confirm that diagnosis.[31] Other patterns that can be seen using conventional chest radiography include ground glass opacities, small nodular opacities, a "shaggy" cardiac silhouette, and poorly defined diaphragm contours,[32] but none of these findings are specific to asbestosis since they are also associated with other infiltrative and fibrotic interstitial lung diseases, such as idiopathic pulmonary fibrosis.[33] In patients who have been exposed to asbestos fibers, the association of these typical radiographic patterns with pleural plaques (usually located between the seventh and tenth ribs in the posteroanterior radiograph)[32] reinforces the diagnosis of asbestosis, but such plaques are not always observed. In some cases, large plaques or diffuse pleural thickening may obscure the interstitial findings.[34]

The chest radiographs of patients with pathohistologically confirmed asbestosis are sometimes interpreted as normal. This phenomenon has been observed in around 10% to 20% of exposed patients. Today, therefore, the clinical diagnosis of asbestosis requires more than a chest radiograph.[35] However, conventional radiography continues to be the first-line diagnostic technique in exposed patients despite its low sensitivity and specificity, and poor interobserver agreement.

High resolution computed tomography (HRCT) using 1-mm collimation has been shown to be more reliable than either conventional radiography or CT for detecting and investigating infiltrative pulmonary changes, including asbestosis, even in asymptomatic individuals with a history of exposure to asbestos. In fact, HRCT has changed the diagnosis of asbestosis by images from both the clinical and the legal standpoint.

The various signs described are seen more clearly in the subpleural areas and lung bases, and some of them are better visualized if additional images are obtained with the patient in a prone position.[36] The following signs are indicative:[34,37,38]

– Septal lines that take the form of linear opacities and correspond to interlobular septal thickening. These opacities can distort the secondary lobules, and when they are numerous the result may be a fine reticular pattern.

– Intralobular lines: linear subpleural opacities, sometimes branching or pointed. These are observed at the centers of lobules and they reflect peribronchiolar fibrosis.

– Curvilinear subpleural lines parallel to the pleura, which take the form of fine subpleural linear opacities a few millimeters thick and of variable length (up to 5-10 cm). In the opinion of some authors these lines represent atelectasis adjacent to pleural plaques.[37]

– Honeycomb pattern: cystic air spaces 0.3 cm to 1 cm in diameter, usually subpleural and with well-defined walls. This pattern indicates fibrosis and bronchiolectasis.

– Parenchymal bands that take the form of elongated opacities a few millimeters wide and up to 5 cm long. These often extend into the pleura, which may be thickened and retracted at the point of contact. Pathologically, these bands represent fibrosis along the bronchovascular sheaths or interlobular septa and are associated with distortion of the parenchymal architecture. They are more common in asbestosis than in other forms of pulmonary fibrosis.

– Rounded atelectasis, which is caused by a collapsed and folded lung, is seen as a mass-like opacity or pseudotumor adjacent to an area of the pleura that is thickened and retracted at the point of contact. The characteristic comet tail sign formed by the vessels and bronchi that penetrate the side of the mass distinguish this abnormality from a peripheral tumor. Rounded atelectasis can occur in any part of the lungs, but is most often found on the posterior face of the lower lobes. It can be unilateral or bilateral and can measure between 2 cm and 7 cm in diameter. The lesion stands out clearly with intravenous contrast material but positron emission tomography is negative. It may develop and progress within a few months or over a number of years.

Both the parenchymal bands and the rounded atelectasis that can be seen in plain chest film and more clearly in HRCT are intrapulmonary reflections of diffuse thickening of the pleura often caused by prior asbestos-related benign pleural effusion. However neither of these signs is specific to asbestos exposure since they are also seen in patients with no such history who suffer from pleural disease caused by trauma, infection, or drugs.[34]

None of the HRCT findings are specific to asbestosis, and no one sign in isolation can be considered diagnostic of this disease. The likelihood of a diagnosis of asbestosis increases with the number of abnormalities identified. Gamsu et al[39] found that the presence in HRCT scans of 3 or more of the signs described above made a diagnosis of asbestosis much more likely. Compared to conventional radiographic findings, HRCT findings provide greater diagnostic certainty and reduce intraobserver variability despite the lack of a set of standard reference images like those used in the ILO system. In the near future, HRCT scanning may replace conventional chest radiography as the imaging technique of choice for diagnosing asbestosis.

Pulmonary gallium-67 scintigraphy is usually positive in patients with asbestosis. This positivity has been attributed to the transepithelial loss of serum proteins that bind to the isotope and their subsequent capture by alveolar macrophages. An increase in epithelial permeability to proteins in asbestosis has been demonstrated with diethylene triamine pentaacetic acid.[34,37]

Lung Function

The following functional abnormalities observed in patients with asbestosis are those typically associated with diffuse interstitial disease: a restrictive ventilatory defect characterized by a reduction in forced vital capacity (FVC) and total lung capacity; and a reduction in carbon monoxide diffusing capacity (DLCO).[34,40]

A somewhat negative correlation has been demonstrated between FVC and the profusion of radiographic small opacities,[34] but a wide range of FVC values are possible with different profusion scores, and patients can have a normal FVC with a 3/3 profusion. An associated obstruction, and even air trapping, may occur in patients who are smokers. The diagnostic sensitivity of lung volume measurement is low,[34,40] and diminished DLCO is seen earlier than decreased lung volumes. In the early stages of asbestosis a decline in DLCO may be the only sign of functional impairment. Furthermore, if diffuse thickening of the pleura is also present, with the added restriction this implies, DLCO will be even lower, even though diffusion per unit volume (KCO, or DLCO/V_{A-a}) will be higher than normal because loss of parenchymal lung function does not subsequently develop.[34]

Other authors have also described a reduction in the elasticity of the lung occurring even before any reduction in lung volumes has been observed. This reduction in pulmonary elasticity is an indication of interstitial lung disease, but it is difficult to measure or interpret in clinical practice.

Exercise testing can detect arterial oxygen desaturation on exertion.[34,41]

It has been suggested that the inflammation and fibrosis caused by the asbestos may obstruct the small airways (reduction in forced midexpiratory flow rate, increase in the alveolar plateau slope of the nitrogen washout curve and in the ratio of residual volume to total lung capacity). In practice, however, standard tests only detect obstruction when the patient is a smoker.[34]

Bronchoscopy and Bronchoalveolar Lavage (BAL)

Endoscopy does not reveal obvious macroscopic abnormalities in patients with asbestosis, but BAL fluid may provide cytologic, biochemical, and mineralogical information in both exposed patients and patients with asbestosis. BAL can provide evidence of alveolitis and reveal the presence of asbestos bodies or fibers, thus ruling out other types of interstitial lung disease.[34,42]

Alveolitis is characterized by a higher total cell count, mainly due to macrophages because of their key role in the pathogenesis of alveolitis), and by a slight and variable increase in neutrophils, eosinophils, and fibronectin. This cellular response is not specific to asbestosis; it is also observed in diffuse interstitial fibrosis and even in heavy smokers.[34] The severity of these changes correlates more with lung function abnormalities, such as low DLCO, than with radiological changes; the greater the number of neutrophils and eosinophils, the lower the DLCO and the poorer the prognosis. High concentrations of fibronectin and procollagen III have also been associated with a poor prognosis.

Lymphocytic alveolitis with an increased CD4+/CD8+ ratio in patients with asbestosis has been described, although this condition is more common in exposed workers who have no clinical or radiological signs of asbestosis but who do sometimes have pleural fibrosis.[34] The inflammatory mediators found in bronchoalveolar lavage are being studied in order to gain a better understanding of the pathogenesis of the disease, but these studies are not yet relevant to clinical practice.[34]

Pathology

Macroscopically, asbestos-related pulmonary fibrosis is indistinguishable from other forms of interstitial fibrosis. Even microscopically at high magnification the appearance of asbestos-related fibrosis is similar to that of idiopathic pulmonary fibrosis, with the fibrosis occurring in the lower lung fields and honeycombing in advanced cases. Since asbestosis always predominantly affects the lower lung fields, it is almost possible to rule out this diagnosis altogether in cases where the fibrosis mainly affects the upper fields.

The only sign that differentiates between asbestosis and diffuse interstitial fibrosis is the presence of asbestos bodies in the lung tissue. At least one asbestos body must be found to establish a diagnosis of asbestosis.[42] The fibrotic component is made up of collagen tissue and inflammatory cells. The pathologist must be sure that the process is diffuse and not simply a local reaction secondary to a tumor, radiation, or other process. This conclusion must be supported by the results of chest radiography and lung function testing.[34]

Asbestos, like other mineral dusts, produces anomalies in the bronchioles and alveolar ducts. The walls of these airways become fibrotic, but this fibrosis is a nonspecific response to various kinds of inorganic dust that is not correlated with the clinical, radiographic, and functional abnormalities characteristic of asbestosis. Interstitial fibrosis is sometimes found in patients with a history of exposure but no evidence of asbestos bodies. In some of these cases mineralogical analysis may demonstrate the presence of asbestos and the process may be considered an occult asbestosis. Much more often, however, mineralogical analysis does not reveal the presence of a higher than normal asbestos burden, and the process must be attributed to another cause.

When there is a history of exposure, most cases of asbestosis are diagnosed clinically on the basis of the typical radiographic and functional abnormalities. Biopsy should only be used in clinically atypical cases. In such cases, the procedure of choice is open biopsy in order to obtain a sufficiently large tissue sample. Specimens acquired using transbronchial biopsy could prove inadequate and give rise to an incorrect or incomplete diagnosis.[34]

Mineralogical Analysis

Mineralogical analysis can provide evidence of accumulated exposure, which is important when work history information is not complete; it can also reveal indirect exposure. Positive results confirm past exposure to asbestos, but negative results do not rule out past exposure. When there is the slightest suspicion of occupational exposure in patients who have been operated on for lung cancer, a systematic count of the asbestos bodies found in the resected lung can confirm the, possibly occupational, asbestos-related etiology. The presence of ferruginous bodies in biopsies from patients with interstitial disease will also serve this purpose. Such analyses can be performed on digested samples of lung tissue using optical microscopy, although analysis with an electron microscope is sometimes preferable.[34,40]

Once fibers have been deposited and retained in the lung, some of them are coated in a proteinaceous material containing iron. This process gives rise to the production of what are called ferruginous bodies (or asbestos bodies if the fiber is asbestos). Asbestos bodies are mainly formed by amphibole fibers and more rarely by chrysotile fibers. A large number of asbestos fibers and bodies are found in the lung tissue and BAL fluid of patients with asbestosis. Conversely, if the number of fibers found falls within the normal range, asbestosis can be ruled out as a diagnosis. Asbestos bodies are rarely found in the BAL of patients without a history of occupational exposure, and if any are found, the concentration is lower than 1.0 per cm^3. De Vuyst and Gevenois[34] found a mean of 121 asbestos bodies in the BAL of patients with asbestosis, while mean values in patients with benign pleural disease and in exposed workers who had no asbestos-related disease were 4 and 5 per cm^3, respectively.

Quantitative analysis of asbestos bodies in lung tissue is the gold standard diagnostic technique. Although reference counts vary considerably between laboratories, most of them agree that the presence of more than 1000 uncoated fibers per gram of dry lung tissue indicates occupational exposure and that in patients with asbestosis concentrations usually exceed 50 000 per gram and many millions of fibers are often found.[34]

While the presence of asbestos bodies in sputum is a highly specific marker of past exposure, it is not an accurate measurement of the burden of asbestos fibers in the lungs.

Fiber Analysis Techniques

The total prohibition in Spain of the use, production, and sale of products containing asbestos fibers (Ministerial Order of December 7, 2001 modifying Appendix I of Royal Decree 1406/1989 dated November 10 restricting the sale and use of certain dangerous substances and preparations, published in Official State Bulletin [BOE] Number 299, dated December 14) in no way implies that such fibers will no longer be found in the air. This is because the prohibition only affects the intentional use of asbestos and not involuntary handling arising from the presence of this material in many places, mainly in the form of insulating material but also in roofing, tanks, and piping. From the point of view of air quality, therefore, whenever asbestos forms part of any materials used in the construction or decoration of a building and such materials are handled in the course of the renovation, repair, or demolition of same, there is a risk that asbestos fibers will be released into the air, making it necessary to measure environmental concentrations.[43]

Measurement of environmental fiber concentrations. Airborne fibers are measured in accordance with Spanish standard UNE 77235 or UNE 77253. These standards basically specify that airborne fibers should be captured in an air filter and then counted and identified in a laboratory using either phase contrast optical microscopy after the filter has been rendered transparent or electron microscopy. The result is expressed as the number of fibers per cubic centimeter of air. In Spain, no limit has been specified to regulate the maximum permitted fiber content of indoor air in non-industrial environments, but such a limit value does exist in other countries, such as France, where the maximum airborne fiber content permitted is 0.005 fibers per cm^3.

Techniques for analyzing the asbestos content of tissue. Several instruments are used to analyze the asbestos content of tissue. The choice of technique or the use of more than a single technique on any particular occasion will depend, apart from the availability of instruments in the laboratory, on the type of analysis to be performed and the information sought.[44-46] The instruments most commonly used in tissue fiber analysis are optical microscopes for counting asbestos bodies and transmission electron microscopes for counting fibers.

Optical microscopy is the technique most often used for the quantitative analysis of asbestos fiber content in environmental samples and for counting asbestos bodies because it is cheaper than alternatives. The disadvantage of optical microscopy is that it is a visual, manual, and statistical technique that requires considerable skill and expertise. The microscope has 2 converging lenses or lens systems, the objective and the ocular lenses, which are mounted in fixed positions at either end of a metal tube of known length. An optical microscope for counting fibers

or asbestos bodies must have Köhler illumination, an achromatic phase-contrast condenser, a stage with XY movement, 10× and 40× lenses with an achromatic numerical aperture of 0.65, a phase ring of not less than 65% and not greater than 85% absorption, and a circular Walton Beckett graticule 100 μm in diameter. Before the asbestos bodies can be counted, all the organic material must be eliminated from the tissue sample, which is generally preserved in 10% formol. A known quantity of tissue is weighed and digested with sodium hypochlorite for 24 to 48 hours. The residue is then centrifuged, diluted with deionized water, and deposited on a cellulose ester filter. The filter becomes a transparent and optically homogeneous specimen that can be used to count the asbestos bodies. All asbestos bodies 5 μm or longer must be counted. The result is expressed as the number of asbestos bodies found per gram of dry lung tissue.

Scanning and transmission electron microscopes, which have higher resolution than optical microscopes, make it possible to detect and observe fibers with a very small diameter and to identify the different fiber types. The main disadvantages of using electron microscopy are the high cost of amortizing the purchase of the instrument and the time required to prepare the samples. The electron microscope is a powerful instrument and it is relatively easy to use. Using an incandescent tungsten filament, the electron gun produces a narrow beam of electrons, which is then focused by a set of electromagnetic lenses to bombard the sample. A vacuum environment of between 10^{-6} and 10^{-7} torr must be maintained to prevent the electrons from colliding with gas molecules and deviating from their proper trajectory. The different types of signals produced when this beam interacts with the sample are as follows: secondary electrons (low energy), back scattered electrons, absorbed electrons, characteristic x-ray radiation, and photons of various energies. The signal of interest is the one produced by the transmitted electrons having an acceleration potential of 100 to 200 kV. For electron microscopy, a known quantity of lung tissue must be weighed, lyophilized, and dissolved in a solution of water and ethanol. The solution is then heated to eliminate the ethanol. After this operation is repeated, the result is once again dissolved in hydrochloric acid, 0.5 N, and the residue is placed on a polycarbonate filter. This filter is then placed on a grid, coated with graphite, and rendered transparent. The technician then inspects the grid and counts the fibers that meet the countable criteria (length >5 μm, width <3 μm, and a length-to-width ratio greater than 3:1). The result is obtained by calculating the number of fibers counted per gram of dry tissue.

Asbestos-Related Pleuropulmonary Diseases

Benign Asbestos-Related Pleural Diseases

Inhalation of asbestos fibers often causes benign pleural abnormalities. This has been demonstrated epidemiologically, by experimental studies involving the introduction of asbestos into the pleural cavity, and also by studying the in vitro response of mesothelial cells when confronted with asbestos. The mechanism by which asbestos fibers cause pleural lesions is poorly understood. It has been suggested that the fibers move mechanically until they reach the lung periphery where they interact directly with the pleura causing lesions and perhaps giving rise to inflammation. An alternative hypothesis is that the fibers reach the pleura indirectly by way of the lymphatic system of the parietal pleura. In any case, although the asbestos lung burden is greater in individuals with benign pleural lesions than in the general population, the pleural deposit is scant and only detectable using electron microscopy. Patients with benign pleural lesions caused by asbestos exposure are more likely to develop asbestos-related neoplastic disease, but it has not been demonstrated that the pleural lesions themselves become malignant.[47]

Pleural plaques. Pleural plaques are circumscribed fibrohyaline thickenings which, almost without exception, affect the costal, mediastinal, and diaphragmatic parietal pleura. Histology reveals these plaques to be acellular hyalinized collagen structures covered with a layer of mesothelial cells. Concomitant pulmonary asbestosis is found in 30% of cases. The few fibers detected in these plaques are, for the most part, chrysotile even though amphiboles are the asbestos fibers most often found in lung tissue. In the urban population in general, the number of pleural plaques found in autopsies increases in proportion to the asbestos burden in the lung. In individuals with a history of occupational exposure, the incidence of pleural plaques is directly related to the intensity of exposure and the latency period. In studies of exposed workers based on plain chest radiography, no plaques have been observed within the first 10 years, 10% of the population developed plaques 19 years after first exposure, and after 40 years plaques were found in up to 58% of workers. In areas where there is environmental exposure to asbestos, such as northern Greece, up to 47% of the population has pleural plaques.[48] Since the presence of plaques is considered to be a reflection of an individual's exposure, radiographic detection of such plaques can be a valuable diagnostic and epidemiological tool.[47,49]

Individuals with pleural plaques are usual asymptomatic. The plaques are predominantly bilateral, and when unilateral mostly affect the left side. Oblique projections facilitate the detection of plaques when conventional chest radiography is used, and HRCT provides a better visualization of both the plaques and the lung. Patients with pleural plaques whose lungs are not affected do not usually present abnormalities in respiratory function except when the plaques are very extensive, in which case a restrictive defect may appear.

Diffuse pleural fibrosis. Unlike pleural plaques, diffuse fibrosis affects mainly the visceral pleura and has no clearly defined margins. The frequency and progression of this condition increase in relation to the

intensity and duration of the asbestos exposure. Histology reveals a collagen deposit with few cells and hyperplasia of mesothelial cells. There is usually subpleural lung fibrosis not exceeding 1 cm in depth.

Functionally, patients present a restrictive ventilatory defect and reduced forced expiratory volume in 1 second (FEV_1), FVC, and total lung capacity, but a normal ratio of FEV_1 to FVC; ventilatory insufficiency is rare. Some patients may present an associated pericardial constriction caused by fibrosis affecting this area. An oblique projection must be included when the imaging technique used is the simple chest radiograph. In addition to the pleural thickening, which tends to affect mainly the intermediate and lower lung fields, parenchymal bands are usually observed in the lung periphery running perpendicular to the thickened pleura in a "crow's feet" pattern. HRCT facilitates better visualization of these abnormalities, and of any associated lesions, such as rounded atelectasis.[50]

Benign pleural effusion. Exposure to asbestos can cause benign pleural effusion. This is the asbestos-related disease that occurs most often in the 20 years after first exposure. In some cases, the latency period is only 10 years, and in general the frequency of this entity is directly related to the degree of exposure.[49]

The symptoms—such as dyspnea and pleuritic chest pain—that benign effusion produces are nonspecific and in many cases the patient may be asymptomatic. The effusion is usually unilateral and more often affects the left side. With respect to diagnosis, no pathognomonic symptoms exist. The pleural fluid is a serous or serosanguineous exudate with a predominance of polymorphonuclear lymphocytic or eosinophilic cells, low concentrations of adenosine deaminase, and negative cytology for malignant cells.[51] Histologic examination of the pleura reveals only nonspecific inflammation, and asbestos bodies are only occasionally found in the pleural tissue. In order to establish a diagnosis of asbestos-related benign pleural effusion, all other causes must be ruled out, especially mesothelioma and metastatic pleural cancer. Therefore, when the effusion persists after the study of pleural fluid performed during the initial assessment, a thoracoscopic examination is advisable. In any case, for the process to be definitively diagnosed as benign, the patient must be monitored for at least 3 years. On long term follow up, pleural effusion recurs in up to one third of patients, 20% develop diffuse pleural fibrosis, and a malignant pleural mesothelioma develops in 5%.

Rounded atelectasis or Blesovsky syndrome. Rounded atelectasis appears in up to 10% of patients. This lesion consists in the entrapment of a peripheral part of the lung by infolding of the adjacent thickened pleura. On HRCT chest scans, the characteristic image is a peripherally sited mass, pleural thickening, and the curved swirl of the vessels and bronchi converging on the pulmonary hilum. This sign therefore makes it possible to differentiate between rounded atelectasis and a neoplasm, making further aggressive diagnostic tests unnecessary in most cases. It is, however, sometimes necessary to order additional diagnostic procedures to rule out malignancy. Most patients with rounded atelectasis have a history of asbestos exposure, but this lesion has also been reported in association with pleural thickening and effusion due to other causes. The lesion may develop and progress within a few months or over several years.[52]

Asbestosis. Asbestosis is a diffuse form of asbestos-related interstitial pulmonary fibrosis[53] that affects both lungs and can be detected by chest radiography. A sufficient interval must have elapsed between the appearance of fibrosis and the asbestos exposure. The latency period between first exposure and the appearance of asbestosis is usually estimated to be between 15 and 20 years, although no consensus has been reached on this subject. There is a clear dose-response relationship between the intensity of the asbestos exposure and the risk of developing asbestosis, meaning that individuals with greater exposure are more likely to develop the disease. Risk most probably differs in relation to the number of asbestos fibers inhaled,[54] although the susceptibility of the individual also plays a role.

1. Incidence. The incidence of asbestosis has not been established with any exactitude. Very few of the epidemiological studies undertaken among exposed workers are completely free of any kind of bias and/or involved following a sufficiently large cohort over a long enough period. The most realistic estimates put the incidence of this disease between 1% and 5% of exposed workers.[3]

2. Pathogenesis. The pathogenesis of asbestosis is not known, although it appears clear that the condition is an inflammatory response to the inhaled agent. This response is progressive, irregularly distributed throughout the lungs, and associated with extensive remodeling and fibrosis of the lower respiratory tract. This chronic process leads to the proliferation of mesenchymal cells, intraalveolar fibrosis, and loss of alveolar capillaries. Except for the presence of asbestos fibers in the lung parenchyma, the histologic alterations are not easy to distinguish from those associated with other fibrosing processes.

3. Clinical and radiographic findings. The symptoms of asbestosis are nonspecific. The most common symptoms are a rather unproductive cough, crackles in the lung bases, and dyspnea in advanced cases. The crackles, which are of the "Velcro" type, are observed in over 80% of patients with asbestosis, and they sometimes occur before any abnormalities are visible in the chest radiograph.[55]

Typically, asbestosis appears on the radiograph as irregular lines in the lung periphery, particularly in the lower lobes. In the early stages of the disease, the central and upper areas of the lung are not affected, while in very advanced cases fibrosis affects both lungs in a generalized

TABLE 4
Differential Diagnosis: Asbestosis and Idiopathic Pulmonary Fibrosis*

	Asbestosis	Idiopathic Pulmonary Fibrosis
Clubbing	±	++
Reduction in DLCO	+	++
Localization by imaging (chest radiography or HRCT)	Lower subpleural zones	Intermediate and upper zones, posterior and anterior
Honeycombing	+	++
Ground glass opacity	±	+
Association with pleural lesions (plaques or thickening)	++	−
Parenchymal bands	+	−
Disease progression	Slow or absent	Variable, can be rapid
Bronchoalveolar lavage	Asbestos bodies ++	Rare or absent

*DLCO indicates carbon monoxide diffusing capacity; and HRCT, high resolution computed tomography. Information from de Vuyst and Gevenois.[34]

manner. Despite the fact that the diagnosis of asbestosis was for a long time based on the abnormalities found in the chest radiograph, this method no longer seems adequate today.[35] In the first place, between 15% and 20% of plain chest radiographs among individuals with asbestosis are normal[56] and, secondly, the advent of HRCT scanning has provided us with interstitial images that were impossible to achieve with conventional chest radiography. The use of 1- to 3-mm collimation in the HRCT scan and improved spatial reconstruction algorithms have made it possible to visualize even very slight abnormalities in the interstitium, thereby facilitating early diagnosis of asbestosis. The most common abnormalities are short interstitial lines (perpendicular to the pleura), a curvilinear subpleural pattern (approximately parallel to the pleura), parenchymal bands, and microcystic patterns. Some authors also report ground glass opacities, although this pattern is much less common. These lesions are similar to those found in histologically proven usual intersitial pneumonia.[33]

The abnormalities are distributed irregularly throughout the lung parenchyma, although there is a clear predominance in both lower lobes. In more advanced stages, however, the disease can affect all the pulmonary lobes, and in the final stages the lungs are indistinguishable from lungs in the final stages of any diffuse interstitial lung disease. Distinguishing asbestosis from idiopathic pulmonary fibrosis can be difficult. The differential characteristics according to de Vuyst and Gevenois[34] are shown in Table 4.

4. Lung function. Like other types of diffuse interstitial pulmonary fibrosis, asbestosis produces a restrictive defect manifest by a reduction in FVC and total lung capacity. These abnormalities are not, however, specific to asbestosis, and they may be absent in the initial and intermediate stages of the disease. DLCO, which is more sensitive but also not very specific, is reduced in 70% to 90% of cases. In any case, a normal DLCO is very uncommon in patients with asbestosis.

5. Diagnosis. Some of the difficulties associated with the diagnosis of asbestosis have not yet been resolved. On the one hand, a confirmed diagnosis of asbestosis can only be obtained by means of a lung biopsy, which is not usually performed. On the other hand, the question should be posed as to whether the mere presence of fibrosis in the biopsy is sufficient evidence to establish a diagnosis, or whether the diagnostic criteria should not also include a certain degree of functional impairment and, if so, what degree of fibrosis and/or functional impairment would be required. Asbestosis, like all diffuse interstitial lung diseases, is a continuous process in which signs and symptoms are scant in the early stages despite the presence of disease.

Notwithstanding these considerations, the clinical diagnosis of asbestosis is currently established on the basis of 2 criteria: the patient's history of exposure to asbestos and the presence of unmistakable signs of diffuse interstitial fibrosis. With respect to the history of exposure, it is important to note that a minimum period of exposure to asbestos is necessary (estimated to be
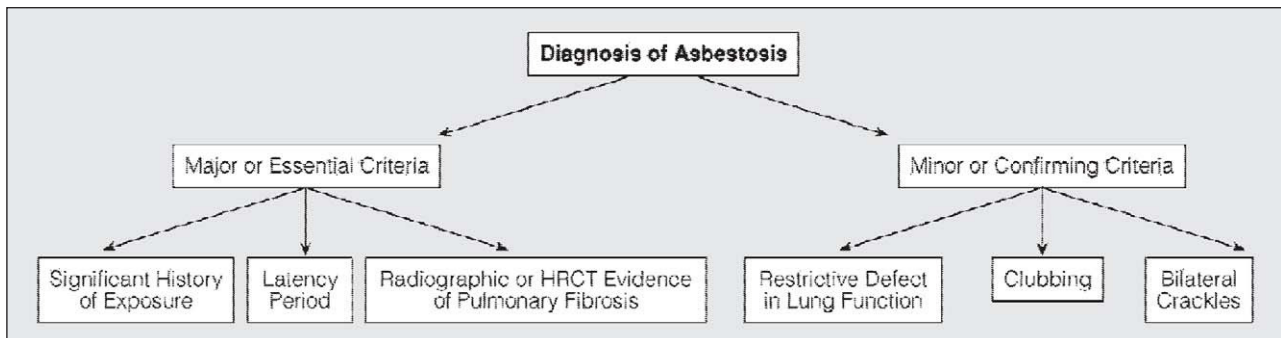

Figure 1. Criteria for the diagnosis of asbestosis. HRCT indicates high resolution computed tomography.

around 5 years) as is a sufficient latency period[2] (estimated to be about 15 years). In general, it is not difficult to detect asbestosis because the patient's work history is usually clear. In some cases, however, diagnosis is more difficult because the patient cannot remember or is not aware of having worked with asbestos. In such cases, the presence of bilateral pleural plaques in the radiograph is a help because these lesions are almost never found in people who have not been exposed.[57] The presence of "Velcro" type crackles and interstitial radiographic involvement of the lower lobes found in conjunction with a reduced DLCO provides sufficient evidence of the unequivocal presence of diffuse interstitial fibrosis in over 90% of cases.[3] If these criteria are fulfilled, histologic confirmation does not appear to be necessary. Conversely, asbestosis can be ruled out if interstitial involvement is not bilateral, even when other signs of asbestos-related pleural disease are present (pleural plaques, rounded atelectasis, etc).

The diagnostic value of the presence of asbestos bodies in sputum and BAL fluid has been debated in depth. The currently accepted view is that their presence is only an indicator of asbestos exposure,[58] and that it is impossible on this basis alone to assert that any pulmonary lesions found were necessarily caused by asbestos fibers.

Although histopathological study provides a firm diagnosis, recent studies have assessed the sensitivity of other methods and the mortality associated with invasive methods. The current preference is diagnosis using noninvasive methods based on several major or essential findings and several minor or confirming observations (Figure 1).[59,60]

6. Asbestosis and the risk of lung cancer. Asbestosis is associated with an increased risk of developing lung cancer. Among workers exposed to asbestos, the incidence of lung cancer is higher among those who develop asbestosis; the increase ranged from 4 times higher in some case series[61] to 6 times higher in others.[62] A higher than usual incidence of lung cancer has also been reported among patients with other interstitial lung diseases,[63] an indication that the factors responsible for the associations observed have not been clearly identified. The degree of fibrosis, the type of asbestos fiber, and whether or not the patient is a smoker all seem to be related factors.[64]

7. Prognosis and treatment. It is generally accepted that asbestosis is a slow and progressive disease. If the disease is diagnosed early and the causal agent is eliminated, survival is conditioned to a larger extent by associated diseases, if any, than by the asbestosis itself. Advanced age, the size of the radiographic lesions, smoking status, and a reduced DLCO are all indications of a worse prognosis.

There is no treatment for asbestosis. Ensuring that the patient no longer enters the contaminated environment is the first step that must be taken, although this action will not stop the progress of the disease. In the advanced stages, treatment with oral corticosteroids can be tried in addition to the usual support measures.

Malignant Asbestos-Related Pleural Diseases

Mesothelioma. Mesothelioma is a tumor originating in the mesothelial layer of the pleural or peritoneal serous membrane. The incidence of this relatively uncommon tumor in European Union countries is approximately 1.5 cases per 100 000 inhabitants every 5 years, with incidence reaching its peak among the cohort 50 to 70 years old. In Spain (according to the scant information we have), pleural tumors are at least 4 times more common than peritoneal tumors, and mesothelioma affects almost 5 times more men than women. This differs from the situation in the United States of American, Canada, and some European countries, where peritoneal involvement is more common than pleural and where both sexes are affected to the same degree.

Localized mesothelioma can be benign or malignant, and its etiology is unknown. Diffuse mesothelioma, on the other hand, is always malignant and was considered an exceptional finding until the middle of the last century. Since Wagner's study of South African workers (1959-1960), mesothelioma has been considered to be a tumor caused by exposure to asbestos and in particular to amphiboles, although in practice this etiology is not clearly proven in almost a third of cases. This failure may be due in part to the existence of undetected environmental exposure—a phenomenon that occurred for many years with erionite in Turkey and tremolite in Corcega and Cyprus—and it is also possible that patients may have forgotten about their occupational exposure to asbestos given that, in most cases, more than 30 years elapse between such exposure and the appearance of the clinical signs of the tumor. In recent years, researchers have studied the association between mesothelioma and simian virus 40. This virus, which is known to have contaminated some lots of poliomyelitis vaccine in the past, has been shown to have a carcinogenic effect on mesothelial cells. Research is also focusing on certain genetic profiles that may predispose some individuals to develop mesothelioma more than others.

There was a noticeable increase in the incidence of mesothelioma during the second half of the last century related to the progressive increase in the industrial use of asbestos. The type of asbestos most likely to cause mesothelioma is blue or crocidolite asbestos, and the least dangerous is the white or chrysotile type (although the latter can contain other more carcinogenic impurities, such as tremolite). Differences in the risk of causing mesothelioma seem to depend more on the

TABLE 5
Suspected Diagnosis of Mesothelioma

Chest pain
Pleural effusion
Thickening or scalloped appearance of pleural plaques
Pain in patients with previously asymptomatic plaques
Work history involving risk and latency period elapsed
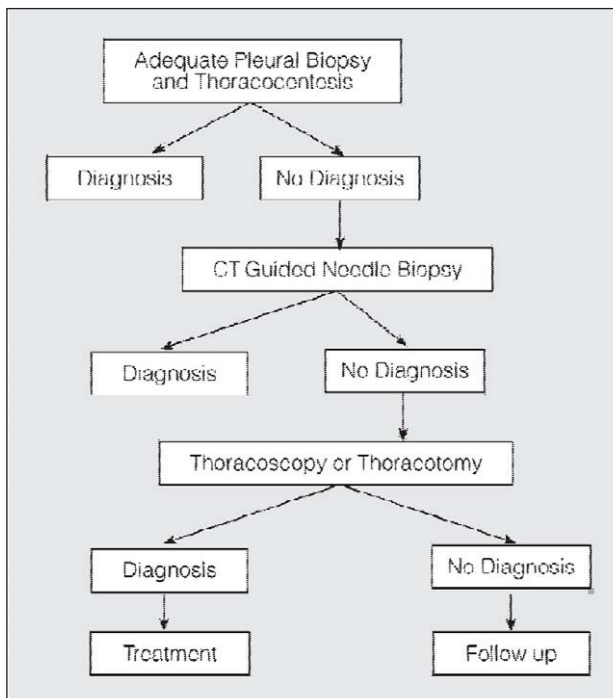Radiographic signs

Figure 2. Firm diagnosis of mesothelioma. CT indicates computed tomography.

physical characteristics of the fibers (length and thickness) than on their chemical composition. This is because of the variations in the capacity of different fibers to penetrate the pleural surface via the airway, and also the fact that some fibers, such as chrysotile, can dissolve slowly in the organism, while others persist. The risk of mesothelioma is proportional to the density of airborne asbestos dust, the duration of exposure, and the time that has elapsed since first exposure to this agent. In general, over 15 years must elapse before this tumor develops.

1. Diagnosis of pleural mesothelioma. Localized mesothelioma is usually asymptomatic, it does not result in pleural effusion, and is generally discovered during a radiographic examination undertaken for another reason. Diffuse mesothelioma, on the other hand, is usually accompanied by a pleural effusion that initially is not distinguished by any special characteristics. The most

TABLE 6
Differential Histologic Diagnosis of Mesothelioma

	Mesothelioma	Metastatic Adenocarcinoma
PAS stain followed by diastase digestion	–	+
Carcinoembryonic antigen	–	+
Keratins	+	–
Calretinin	+	–
Vimentin	+	–
Long slender microvilli (by electron microscopy)	+	–

common clinical finding is chest pain, which, although usually slight in the early stages, is persistent and slowly progressive and not clearly pleuritic in nature. In the early clinical stages, pleural thickening is not visible on the chest radiograph, although the presence of pleural plaques (relatively fine with frequent and visible calcification especially in the diaphragm and the lower half of the costal pleura) may have been visible for years. The development of a mesothelioma should be suspected if an increase is observed in the thickness or the scalloped appearance of these pleural plaques, or if pain develops in a patient who has had asymptomatic plaques for a long time. However, the presence of pleural effusion neither confirms nor rules out a diagnosis of mesothelioma, since it may also be the result of a benign asbestos-related pleuritis (Table 5).

The typical macroscopic appearance of evolved mesothelioma is a marked thickening that connects the 2 pleuras, encasing the lung as it extends throughout the pleural cavity and the pericardium. Mesotheliomas are several centimeters thick and penetrate into the lung parenchyma, especially through the pulmonary fissures. In relatively early stages, mesothelioma takes the form of multiple small nodules, which initially affect the costal pleura and then spread to the visceral pleura and progressively coalesce. Spread of the process to the visceral pleura and invasion of the lung, diaphragm, or mediastinum significantly worsen the prognosis for these patients. It is not unusual to find benign pleural plaques in association with tumoral nodules.

A firm diagnosis of mesothelioma can only be obtained through the histology of a sample obtained by pleural biopsy. The specimen must be sufficiently large because of the difficulties associated with the histology of this type of tumor, in particular the great similarity between malignant epithelial mesothelioma and metastatic pleural adenocarcinoma.

Mesothelioma has traditionally been divided into the following 3 histologic categories: epithelial, fibrous (sarcomatous), and mixed. In practice, all mesotheliomas are mixed to a greater or lesser degree. In samples taken from autopsies or thoracotomies (the latter are now rare given the increasing use of endoscopic techniques), mixed mesotheliomas predominate, while epithelial mesotheliomas predominate in samples obtained from biopsies. This is because it is much more difficult to assess the fibrous component in small biopsy samples.

2. Additional techniques used to diagnose mesothelioma. Histologic diagnosis is difficult. Pleural infiltration or metastasis of a lung tumor must always be ruled out, and all radiographic and endoscopic images must be evaluated in light of the patient's history (in particular the work history). While the histology report may be very indicative, especially when paraaminosalicylic acid staining followed by diastase digestion is negative (in this respect mesothelioma differs from metastatic adenocarcinomas in which this result is often positive), immunohistochemical study is currently

common practice. In mesothelioma, this study will be negative for carcinoembryonic antigens and positive for keratins, calretinin, and vimentin. In cases where diagnosis is particularly difficult, an electron microscopy study is recommended because this technique can reveal the presence in the tumor cells of abundant long slender microvilli characteristic of the mesothelium. In most cases, the combination of histologic, clinical and macroscopic (thoracoscopic) findings supported by other techniques will provide the evidence needed to establish a diagnosis of mesothelioma (Table 6).

The results of pleural fluid cytology are particularly confusing in mesothelioma for 2 reasons: the difficulty of differentiating between mesothelial cells reactive to the inflammatory pleural process and genuinely malignant mesothelial cells; and the similarity between malignant epithelial mesothelioma and adenocarcinoma. Pleural needle biopsy also tends to pose difficult diagnostic problems owing to the small size of the samples obtained. It is currently considered that thoracoscopy or thoracotomy are necessary to obtain adequate biopsies; thoracoscopy is a less aggressive and more economical technique, which can be performed under local anesthesia in most cases. However, in certain cases—those in which the mesothelioma involves little or no effusion—percutaneous puncture of the pleural masses guided by ultrasound or computed tomography scan should be considered (Figure 2).

3. Treatment of pleural mesothelioma. Radical surgical treatment is an option that can only be considered in the early stages of the disease when the tumor is confined to the costal or diaphragmatic pleura. This is an exceptional situation since mesothelioma is usually diagnosed in the later stages of the disease. Therapeutic measures are therefore mainly palliative, basically taking the form of pain control since this is finally the dominant and persistent symptom reported by these patients. Neither chemotherapy nor radiation therapy have been shown to be effective, and the only recommended use for localized radiotherapy is when it is applied directly to the area where a needle has been introduced because of the tendency of this tumor to invade the needle trajectory. Nor has intrapleural immunotherapy with gamma interferon or interleukin 2 been shown to be effective. Once again, these techniques are only useful when the mesothelioma is found in an early stage, which does not often happen in clinical practice.

When radical treatment of a mesothelioma in a relatively early stage is under consideration, what is generally required is a combination of very aggressive surgery (pleuropneumonectomy, partial resection of the pericardium, diaphragm, and sometimes even part of the chest wall) together with radiation therapy and even subsequent chemotherapy (multimodality treatment); acceptable results have been reported with this regimen in selected case series.[65,66] However, since asymptomatic tumoral infiltration into infradiaphragmatic structures often occurs, the extent of the tumor should be studied

carefully before surgical treatment of mesothelioma is considered. The method of choice for this study is a combination of HRCT scanning and positron emission tomography.[67] The prognosis for survival in patients with pleural mesothelioma is highly variable, but it is not uncommon for patients to survive more than 5 years after diagnosis without any kind of radical treatment. This is much more common in epithelial mesotheliomas because the prognosis for patients with malignant fibrous mesotheliomas is worse. In recent years, an increasing value has been accorded to positron emission tomography as a prognostic technique in mesothelioma, and it has been shown to be a better marker of disease aggressiveness than the histologic grade of the tumor.[68]

Lung cancer and other neoplastic diseases. While smoking is the primary cause of bronchopulmonary neoplasms, certain agents present in the workplace, such as asbestos, also play a role in the pathogenesis of these tumors. In the laboratory, asbestos has been shown to be capable of causing chromosomal alterations and mutations in mammalian cells,[69,70] and this inorganic fiber has been classified as a carcinogen by the International Agency for Research on Cancer since 1979. The increased risk of bronchopulmonary neoplasms in individuals with occupational exposure to asbestos has been evidenced by observational studies,[71,72] although some authors have suggested that the incidence of such cancers would only be high in exposed patients with asbestosis.[73-76] However, various authors have reported that the increase in the frequency of cancer is not restricted to patients who already have asbestos-related pulmonary fibrosis, but rather that it affects all those with occupational exposure to asbestos fibers whether or not they have asbestosis.[77-81]

The carcinogenic synergy that exists between tobacco and asbestos means that patients with a history of contact with this inorganic fiber and a history of smoking have a very high risk of developing bronchopulmonary cancer at some time in their lives,[82-84] and current evidence suggests that the increase in risk is multiplicative.[85-87]

In the United States of America it has been estimated that slightly more than 5% of cases of bronchopulmonary cancer are caused by asbestos,[88] and higher percentages of asbestos-related bronchopulmonary cancer have been found in residents of some parts of Europe. In Finland, it has been estimated that 19% of cases observed were attributable to asbestos exposure,[89] with a greater risk of adenocarcinoma than squamous carcinoma, and figures of between 10% and 20% have been reported in Holland[90] and in the north of Italy.[91] Recently, Badorrey et al[27] carried out a cross-sectional study in Spain of 82 patients with bronchopulmonary cancer and 53 patients with no pleural or pulmonary disease. They identified occupational asbestos exposure by way of a questionnaire and determined the concentration of asbestos bodies in BAL or lung tissue. A concentration of asbestos bodies greater than 1 per milliliter or 1000 per gram was considered to be
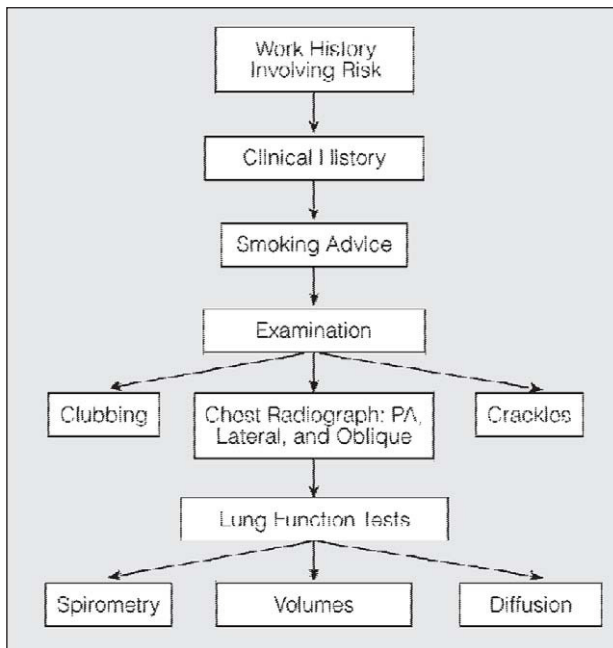
Figure 3. Minimum requirements for periodic health checkups in workers exposed to asbestos. PA indicates posteroanterior.

marker of a high asbestos concentration in lung tissue. In univariate analysis using logistic regression, the diagnosis of bronchopulmonary cancer was associated with smoking (odds ratio, 10.10; 95% CI, 3.50-29.13) and with occupational exposure to asbestos (odds ratio, 3.69; 95% CI, 1.39-9.77). The association with asbestos exposure remained statistically significant when the model was adjusted for smoking. The same study concluded that 4% of the bronchopulmonary neoplasms in Spain are caused by the synergistic action of asbestos and smoking, and that occupational exposure to asbestos doubles the risk of developing this type of cancer.

It is, therefore, estimated that asbestos-related bronchopulmonary cancer, which currently accounts for 5% of bronchopulmonary neoplasms diagnosed in Spain, may increase in the coming decades owing to the common occupational exposure to this inorganic carcinogen during the second half of the twentieth century in light of the prolonged latency period

TABLE 7
Criteria for Undertaking High Resolution Computed Tomography in Periodic Checkups of Workers Who Have Been Exposed to Asbestos

Suspicion of pulmonary parenchymal disease on conventional radiograph
Changes in the parenchyma since the previous checkup
Increase in the thickness or extent of plaques or pleural thickening
Pleural pain in patients with previously asymptomatic pleural plaques
Abnormalities in lung function tests
A greater than normal deterioration in the results of lung function tests with respect to previous checkups

preceding the development of neoplasms in exposed individuals.[92] Cancer may develop in exposed individuals whether or not they present asbestosis, although the risk is greater in those with asbestosis. This probably reflects the larger doses of asbestos inhaled by patients with asbestosis than by exposed subjects with no disease in the lung parenchyma. Tobacco acts as a carcinogen in synergy with occupational asbestos exposure, and the effect is multiplicative. This means that it is particularly important to ensure that workers subject to occupational exposure to asbestos stop smoking as soon as possible. All types of asbestos are carcinogenic. Asbestos can cause any type of cancer, although the most common type is adenocarcinoma.

Prevention

Prevention measures can be classified as either technical or medical. Technical prevention refers to the elimination of exposure to asbestos. All new use or application of asbestos is now banned in Spain by the Ministerial Order of December 7, 2001. In this matter, Spain enacted legislation before the deadline date (January 1, 2005) specified by the European Union Directive. The only exceptions are the demolition sector, for which the regulations define special protection measures, and the chloralkali manufacture sector (asbestos diaphragms used in the production of chlorakalis). Medical prevention mainly takes the form of antismoking campaigns targeting all workers who are or have been exposed to asbestos.

In order to ensure early detection of asbestos-related diseases, a program of periodic checkups of exposed workers has been designed and, in view of the long latency period, any such program must include retired and unemployed workers with a history of exposure. The required medical examinations and timetable are stipulated in the Protocol of Specific Asbestos-Related Health Monitoring drawn up by the Interterritorial Health Council's Commission of Public Health (Comisión de Salud Pública del Consejo Interterritorial de Salud), which defines the necessary minimum requirements for periodic checkups of exposed or previously exposed workers (Figure 3). Since these workers must undergo periodic checkups, including a control radiograph every 3 years if they are asymptomatic and annually if they have benign pleural disease, HRCT is not always indicated because of the high cost and the higher dose of radiation involved. Criteria for including HRCT scans in a periodic checkup can be established, such as those shown in Table 7.

Legislation on Exposure to Asbestos Fibers

Legislation applying to asbestos fiber exposure relevant to Spain is listed in chronological order:

– The ILO Convention No.162 concerning safety in the use of asbestos.

– Spanish Ministerial Order of October 31, 1984: regulations governing work involving the risk of asbestos exposure (Official State Bulletin (BOE) of November 7, 1984).

– Spanish Ministerial Order of January 7, 1987: additional standards regulating work involving the risk of asbestos exposure.

– Resolution of the Spanish Department of Labor (Dirección General de Trabajo) dated September 8, 1987 concerning applications for official certification submitted by laboratories specialized in the determination of asbestos fiber content.

– On September 19, 1983 the Official Journal of the European Union (OJEU) published Council Directive 83/477/EEC on the protection of workers from the risks related to exposure to asbestos at work (second specific Directive arising from Article 8 of Directive 80/1107/EEC).

– On March 19, 1987 the OJEU published Council Directive 87/217/EEC on the prevention and reduction of environmental pollution by asbestos.

– Resolution of the Spanish Department of Labor (Dirección General de Trabajo) published in the BOE dated February 20, 1989) regulating the reporting of environmental and medical records for the control of asbestos exposure.

– Spanish Royal Decree 108/1991 dated February 1, 1991 on the prevention and reduction of environmental pollution by asbestos.

– Spanish Ministerial Order dated July 25, 1993. This Order modifies Articles 2.3 and 13 of the Ministerial Order of October 31, 1984, which established the regulations on work involving the risk of asbestos exposure, and Article 2 of the Ministerial Order of January 7, 1987, which established additional regulations, bringing Spanish legislation into line with Council Directive 91/382/EEC of June 25.

Current Spanish Legislation:

– Order dated December 7, 2001 modifying Appendix I of Royal Decree 1406/1989 dated November 10, which restricted the sale and use of certain dangerous substances and preparations. The use of asbestos is banned with 2 exceptions: the demolition sector and the manufacture of chloralkalis (asbestos diaphragms used in the manufacture of chloralkalis).

– Directive 2003/18/EC of March 27, 2003 issued not only by the Council but also by the European Parliament and published in the OJEU of April 15, 2003 (L97/48), which is at present pending transposition into Spanish law.

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