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Asbestos-associated disease: a review

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Asbestos and its potential for adversely affecting health remain a source of concern to several sectors of society. Since it rarely occurs in the absence of occupational exposure to asbestos, and because it is potentially preventable, asbestosis was recently defined as a reportable occupational disease in Texas. An overview of the cardinal characteristics of the asbestos minerals and their associated health effects is presented. The role of the primary physician in diagnosis and counseling of individuals with asbestos-associated diseases is addressed.

KEY WORDS: ASBESTOS, ASBESTOSIS, OCCUPATIONAL DISEASE REPORTING.

The occupational lung diseases are recognized by the National Institute for Occupational Safety and Health (NIOSH) as heading the list of the ten leading occupation-related conditions in this country (1). When one considers prevalence, potential disability, premature death, and preventability, asbestos as a cause of pulmonary disease continues to be a source of concern to industry, labor, government, and the general public. This is heightened by different medical, sociopolitical, and economic considerations.

In 1985, asbestosis, one of the asbestos-related diseases, was defined as one of the four reportable occupational diseases in Texas (Texas Civil Statutes, Article 5182C) (2). The other three reportable conditions are elevated adult blood lead levels, silicosis, and acute occupational pesticide poisoning (3). This review is one of a series of papers on the reportable occupational diseases in which an overview of the historical, epidemiologic, mineralogical, pathological, and clinical features of asbestosis and the spectrum of asbestos-related conditions or diseases is presented.

Modern history

Asbestos is a term that refers to a group of naturally-occurring fibrous hydrated silicate minerals, useful to man because of their properties of enhanced strength, flexibility, and resistance to physical and chemical insults. It was used sporadically for production of purses and lamp wicks for hundreds of years. Widespread production and use of asbestos began in the late 19th century with the introduction of the steam engine. Unique properties of asbestos—flexibility and virtual indestructibility—were unmatched at the time by any other mineral or man-made fiber and quickly led to its use in the manufacture of a long list of construction materials and textiles, including cement, insulation products, friction materials, electrical appliances, and protective garments. Worldwide production and use of as-

bestos increased dramatically until the mid-1970s when concern regarding health effects of asbestos and the implementation of strict regulatory standards resulted in a decrease in annual use (from approximately 800,000 metric tons used in the United States in 1973 to 210,000 metric tons in 1983). Worldwide cumulative production of asbestos products, however, has continued and it is estimated that approximately 30 million metric tons of asbestos are still in use in this country (4).

Isolated case reports of pulmonary fibrosis in heavily exposed asbestos factory workers appeared as early as 1906 (5) and increased rapidly thereafter (6). Although an association between asbestos exposure, asbestosis, and lung cancer was suspected as early as 1935 (7), firm epidemiologic evidence inferring causality was not reported until 1955 (8). In 1960, a causal association between asbestos exposure and mesothelioma, a malignant and invariably fatal tumor of the pleura and/or peritoneum, was reported (9) and thus further expanded the spectrum of asbestos-related diseases.

Asbestosis first became a recognized compensable disease in 1931, in Great Britain under the Workmen's Compensation Act. In the United States, compensation was first awarded to an asbestos weaver in 1927, through the Massachusetts Industrial Accident Board (10). The extent to which occupational diseases are covered in the United States varies according to each state's workers compensation laws. This inconsistency has led to numerous cases being argued via tort litigation in the courts.

Initially, most cases of asbestosis described were limited to workers in the mining, milling (11), and manufacturing (12) sectors. End-product users (eg, insulators, pipefitters, shipyard workers, etc), were not regularly reported as being at risk of asbestosis until the late 1950s and early 1960s (13), although isolated cases in this sector had been described as early as 1934 (6). From a medicolegal standpoint, the asbestos product use sector is of great interest, since the numbers of exposed workers in these occupations are now considered to substantially outnumber those in the mining, milling, and manufacturing sectors. In the United States, it has been estimated that over 27 million persons have been occupationally exposed to asbestos since 1940 (14). The potential medical, economic, and legal implications of these figures are readily apparent.

Implementation of regulatory measures and safe workplace practices paralleled scientific knowledge; the measures taken initially, such as those of the US Public Health Service, however, were limited and left up to industry to implement and enforce (15). A major step towards stricter workplace regulation took place in 1970 with the passage of the Occupational Safety and Health Act and the subsequent creation of the Occupational Safety and Health Ad-

is the controversy associated with the relationship of rheumatoid arthritis and malignancy. While investigators from Great Britain have reported an increased risk for lymphoproliferative disorders in patients with rheumatoid arthritis (6,7), studies from the United States have failed to find a significant association (8,9). Furthermore, our patient had received azathioprine (Imuran) and methotrexate for treatment of his rheumatoid arthritis in the three years prior to the discovery of lymphoma. Presentation of stage III malignant lymphoma as nocturnal lower leg pain is unusual.

The patient in case 4 presented with unilateral sacroiliitis interspersed with periods of remission. Sacroiliitis is most commonly seen in inflammatory spondyloarthropathies. Although pure unilateral sacroiliitis may be seen in seronegative spondyloarthritis, it is more suggestive of joint infection or neoplasm (10). Causes of unilateral sacroiliitis are listed in Fig 1. Of the infectious agents causing unilateral sacroiliitis, staphylococcus is most common; in intravenous drug abusers *P aeruginosa* is commonest. Unilateral sacroiliitis caused by *Mycobacterium tuberculosis* in a young man in continental North America is unusual. The initial evidence and closed-needle biopsy had suggested a diagnosis of malignant lymphoma, and the correct diagnosis was made after open biopsy and tissue cultures for mycobacteria. This stresses the importance of tissue culture in all cases suspected of tuberculous infection; staining for mycobacteria is not adequate to exclude tuberculous infection (11).

Some diseases such as syphilis, diabetes mellitus, and tuberculous infections are known to be great mimics. Various malignancies can present in atypical fashions. Pain is a common symptom in rheumatic diseases and also in patients with malignancy. Physicians should stay alert to the possibility of lymphomatous disorders masquerading as rheumatologic diseases. This is important not only for correct diagnosis but because of major differences in the treatment and prognosis of these disorders.

1. Causes of unilateral sacroiliitis

Infection (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus*, pneumonococcus, *Escherichia coli*, *Gonococcus*, *Mycobacteria*, fungi)

Malignancy

Osteomyelitis

Ankylosing spondylitis

Psoriatic arthritis

Reiter's syndrome

Inflammatory bowel disease

Degenerative joint disease

Rheumatoid arthritis

Gout

Still's disease

Familial Mediterranean fever

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ministration (OSHA) in the Department of Labor. OSHA first regulated asbestos in 1971, setting a permissible exposure limit of 12 fibers per cubic centimeter of air (f/cc). Since then the level has been progressively lowered to the current threshold limit of 0.2 f/cc (16). Present legislation specifies standards, not only on levels in maritime and general industry, but also for the construction sector, with specific norms for asbestos abatement projects, since these activities are considered to pose the potential for acute exposure to hazardous levels of dust.

Recognition of asbestos-related diseases has in recent times led to concern regarding the potential for population exposure to already existing asbestos in public buildings, particularly in schools. Legislation set forth by the Environmental Protection Agency (EPA) required all US schools to examine their facilities for asbestos-containing materials and, if any were found, to notify both parents and employees (17). Subsequently, guidelines for dealing with asbestos, if found, were described (18). Although cases of mesothelioma and benign pleural changes have been described as a result of nonoccupational exposure, these have generally been limited to immediate family members of asbestos workers, or to individuals living near asbestos plants or naturally occurring asbestiform fiber deposits (19–22). Even so, cases of mesothelioma have been described in which no obvious risk factors were identified. Epidemiologic data regarding the long-term effects of exposure to low levels of asbestos, such as those encountered in schools, are sparse. Risk assessment of population exposure in these settings using measurements of fiber levels inside public buildings, extrapolation of data from occupational cohorts, and mathematical models has been performed recently. Estimates of excess lung cancers and mesotheliomas have varied in precision, mainly because of differences in underlying assumptions regarding levels of occupational exposure in the different cohorts analyzed (4,23–25).

Mineralogy and the asbestos chain

The asbestos minerals are classified into two distinct classes, serpentines and amphiboles. The serpentine class contains one member, chrysotile (white asbestos), which accounts for 90% of commercial asbestos produced worldwide. In the United States, 95% of the commercial use of asbestos has involved chrysotile. There are five main types of amphiboles: crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite, actinolite, and tremolite. Serpentine asbestos fibers, as their name implies, are long, wavy, and very flexible, whereas the amphiboles tend to be shorter and straighter; these properties are taken into account in the manufacture of asbestos-containing products. The major asbestos mining countries are Canada (which mines almost exclu-

sively chrysotile), South Africa (the major producer of crocidolite and amosite), and the Soviet Union (26).

Although numerous trades in industry have dealt with asbestos, the "asbestos chain" can be broadly categorized as described in Fig 1 (16). Knowledge of these different sectors of the asbestos chain is important because of differences in the nature of the exposure and the concomitant risk of disease. Most occupational asbestos exposure in Texas has occurred in end-product use.

Determinants of asbestos-related health effects

Not all individuals exposed to asbestos will develop asbestos-related disease. Factors relating to both environment and host must interact to create the necessary conditions for a pathologic response. Among these, we can distinguish fiber characteristics, individual susceptibility, and the nature of the exposure.

It is mandatory for fibers to be *respirable* (i.e., of a size that, after inhalation, can reach respiratory bronchioles and alveoli). In general, this capability is limited to fibers with an aerodynamic diameter of 3 μ m or less, since larger diameter particulates tend to be trapped in more proximal airways. In addition, animal experiments suggest that asbestos fibers with a large *aspect ratio* (length:width ratio) appear to have more pathogenic potential than shorter, thicker ones (4). Similarly, at least with respect to mesothelioma, there is evidence of a differential risk gradient by *fiber type* (28–32), with crocidolite posing the greatest risk, followed by amosite and, at the lower end of the scale, chrysotile and anthophyllite.

Once a fiber has reached the alveolar level, it must persist long enough to cause an effect. Foreign particles in the lung are typically handled by two basic lung defense mechanisms, the mucociliary escalator and the alveolar macrophage or scavenger

1. Common sources of asbestos exposure

Mining and milling, in and around either open-faced or underground mines. In this stage, fibers are for the most part initially intact in the rock, but subsequent crushing in the mill may generate large amounts of dust.

Primary manufacturing, where raw asbestos fibers are received, introduced, and processed to make asbestos products such as cement, sheet, and paper.

Secondary manufacturing, where products are received from primary manufacturers and further processed (including sawing, pressing, and drilling) to fabricate other intermediate or finished products.

End-product use, involving the application of products, generally in the construction, insulation, electrical, automotive, and shipbuilding industries.

Nonoccupational or environmental exposure. Since all persons may have some asbestos fibers in their lungs from general environmental levels (27), the question of what constitutes significant environmental exposure is still being debated.

cell. The macrophage phagocytizes the particle and is subsequently transported away (cephalad) from the area by either the mucociliary escalator or drainage to the regional lymph nodes. With asbestos fibers, this task may be complicated by the fibers' peculiar dimensions and resistance to destruction, making them harder to engulf. Some of the fibers are eventually coated with an iron protein material which confers a club- or beaded-like appearance to the fiber (asbestos body). Evidence from in vitro and animal experiments suggests that these coated fibers have been rendered less reactive than naked ones (33-35). Data have also shown that inhaled chrysotile may in part disappear over time from the lung, possibly due to leaching of minerals and fiber fragmentation and dissolution, whereas the amphiboles tend to persist in both coated and uncoated states (36,37). Asbestos bodies have been found not only in persons occupationally exposed to asbestos, but also in lungs of presumably nonexposed urban residents, examined at autopsy, although generally in much smaller numbers (27). Therefore, it is believed that the presence of asbestos bodies in the lung is a marker of asbestos exposure, not disease.

This information suggests that for exposure to asbestos to produce disease, there must be some quantity of retained uncoated asbestos fibers, possibly related to overwhelming of the normal lung defense mechanisms. Data concerning the pathogenesis of parenchymal injury at this stage are uncertain, but currently favor the occurrence of an inflammatory response and release of cytotoxic enzymes, initially at the peribronchiolar level, which can ultimately lead to fibrosis (38). Bronchoalveolar lavage analysis has revealed the presence of increased numbers and types of inflammatory cells, as well as some immunological changes in asbestos-exposed subjects both with and without asbestosis, although many of these abnormalities are not specific to asbestos exposure (39-41).

Several studies have noted that the prevalence of smoking among asbestos exposed individuals is quite high. In vitro and in vivo studies have shown that particle clearance is impaired in the presence of cigarette smoke, and epidemiologic data have found that the risk of lung cancer is increased markedly among asbestos-exposed smokers (42-44). In addition, smokers are at increased risk of other lung diseases (eg, emphysema) which are independent of an association with asbestos. Therefore, smoking may also be responsible for some of the symptoms and lung pathology present in asbestos-exposed subjects and needs to be taken into account during their clinical evaluation (45).

The nature of exposure to this mineral is important as a determinant of disease. When evaluating a potential causal link between a suspected toxin and an adverse effect, the demonstration of a dose-

response relationship constitutes evidence in favor of the toxin's being the cause of that effect. Numerous studies have shown dose-response relationships between asbestos exposure and the established asbestos-related conditions and diseases (46). Autopsy series document correlations between lung fiber content and asbestosis and mesothelioma (46-48). The ability of epidemiological studies to demonstrate dose-response relationships depends in part on their precision in defining both exposure levels and disease. Unfortunately, the appropriate exposure data are not always available because of the long latency period between asbestos exposure and onset of disease, the general lack of workplace dust level measurements, and the marked variation in individual exposures (14). This limitation is particularly true when evaluating the risks in end-product users. Less direct measures of exposure, such as years since onset of first exposure, duration of exposure, and job type provide in some instances a rough correlation between dose and response (46).

Nonmalignant asbestos-related pathology PLEURAL CHANGES

Asbestos exposure is associated with different types of nonmalignant processes involving the lungs and pleura. For medical and compensation purposes, it is necessary to carefully differentiate those changes associated with functional impairment and disability from processes not generally leading to disease or disability.

Nonmalignant asbestos-associated pleural changes may be of three types: circumscribed pleural thickening (plaques), diffuse pleural thickening, and pleural effusion. Pleural plaques are irregularly rounded, circumscribed lesions that are characteristically bilateral and most commonly appear on the lower posterolateral aspects of the parietal pleura and central tendinous portion of the diaphragm. An exposure-response relationship has been demonstrated between frequency of plaques and duration of exposure and years since onset of first exposure; plaques correlate less well, however, with cumulative exposure (49). Plaques are uncommon in subjects with less than 20 years elapsed since first exposure and have been reported in persons with nonoccupational exposure to asbestos (50).

Macroscopically, pleural plaques appear as ivory-colored or grayish-white elevated, localized areas on the parietal pleura. The surface of pleural plaques is generally smooth, but often can be nodular. Infrequently, calcification may be visible to the naked eye and tends to correlate with increasing years since first exposure as well as with the age of the plaque. Microscopically, plaques are composed of collagen fibers most often arrayed in a basket-weave pattern. Cellular elements are scarce, and calcium

deposition at this level is common.

Coated asbestos fibers (asbestos bodies) have not been described in pleural plaques. Likewise, uncoated fibers are not visible on light microscopy of routinely prepared plaques, but have been reported when studying ashed specimens (51).

Radiographically, pleural plaques may be the most frequent asbestos-related abnormality described in both cross-sectional and longitudinal studies (50,52); prevalence is even higher at autopsy (53). On the radiograph, pleural plaques are most commonly seen along the lateral aspects of the mid-third of the chest wall and on the diaphragm. They do not involve the apices or costophrenic angles unless they are very extensive. Plaques on the chest wall can appear either in profile or en face, and their presence can often be enhanced with the use of oblique films (54). These lesions may or may not be calcified, but when present, calcium deposition tends to appear in the center of the lesion. The radiographic appearance of pleural plaques can be confused with a variety of radiologic shadows, including those related to subpleural fat, companion shadows, rib fractures, post-thoracotomy pleural thickening, serratus anterior muscle, or previous emphysema.

Circumscribed pleural plaques are asymptomatic. Epidemiologic studies, in general, have not found consistent associations between these changes and clinically significant lung function abnormality. Similarly, the presence of pleural plaques among asbestos workers does not appear to be an independent risk factor for either parenchymal fibrosis or cancer, when adjusted for age and exposure (55-57). At present, no evidence exists that these plaques degenerate into mesothelioma. Because of the current lack of evidence associating pleural plaques with adverse health effects, it is believed that pleural plaques indicate exposure to asbestos, but not asbestos-associated disease. Use of the term "pleural asbestosis" is discouraged, in that it may contribute to confusion with other asbestos-associated processes that do have functional consequences.

Diffuse pleural fibrosis may be detected in some asbestos workers, although it is less common than circumscribed plaques. Differentiation of pleural fibrosis from pleural plaques is important from both a medical and a legal perspective. Pathologically, diffuse pleural fibrosis consists most commonly of a variable degree of thickening of the visceral pleura. Its pathogenesis is unclear, but it can appear adjacent to areas of parenchymal fibrosis and possibly as a sequel to asbestos-related pleural effusions. Radiographically, diffuse pleural fibrosis may also appear *in profile* or *en face*. *In-profile* changes are manifested by obliteration and thickening of one or both costophrenic angles, tapering cephalad. *En face* diffuse pleural thickening casts a milky haze over the

mid- and lower-lung fields and may complicate evaluation of the underlying parenchyma. Computerized tomography of the chest can aid in its detection (58).

Severe diffuse pleural fibrosis independently may cause abnormal lung function, characterized by a decrease in lung volumes and forced vital capacity. In some cases, unilateral or bilateral decortication has been necessary because of severe symptomatic extraparenchymal restrictive disease (59). When evaluating diffuse pleural fibrosis, one should also consider other etiologies such as scarring secondary to prior surgery, trauma, or infection.

Nonmalignant pleural effusions are the earliest asbestos-associated changes to manifest themselves, not infrequently appearing in workers less than ten years since first exposure. They are generally small, and thoracentesis yields an exudate that may be blood-tinged. The effusions are usually unilateral, but can recur and alternatively involve the opposite side. Although often asymptomatic, asbestos-exposed individuals may present with pleuritic pain and dyspnea, with or without an accompanying fever. The effusions tend to resolve spontaneously, although occasionally they persist for long periods of time. Since the effusion itself is nonspecific, other conditions associated with exudative effusion must also be considered, including differentiation from mesothelioma (60).

ASBESTOSIS

Asbestosis refers to a diffuse interstitial lung fibrosis which results from significant asbestos exposure. Of the nonmalignant asbestos-associated diseases, it is the only one which is a reportable occupational disease in Texas (2). When it occurs, the fibrosis develops insidiously and generally after a latency period of usually 20 years and may progress after cessation of exposure. In epidemiologic studies of those industrial sectors where dust levels have been available for some time (ie, mining, milling, and manufacturing), good dose-response relationships

2. Asbestos-associated conditions

	Marker of Asbestos Exposure	Asbestos-associated Disease
Nonmalignant:		
Asbestos bodies	Yes	No
Pleural plaque	Yes	No
Diffuse pleural fibrosis	Yes	Yes
Pleural effusions	Possibly	Yes
Asbestosis	Yes	Yes
Obstructive airways disease	No	Possibly*
Malignant:		
Bronchogenic carcinoma	Possibly	Yes
Mesothelioma	Yes	Yes

*Although unlikely to be of clinical significance.

between duration or intensity of asbestos exposure and asbestosis have emerged (61–63). Similarly, autopsy series have revealed a rough correlation between lung asbestos fiber content and parenchymal fibrosis (48). Unfortunately, the finding of similar dose-response associations in the end-product use sector is made difficult by the lack of adequate exposure data. To date, there is no firm evidence that non-occupational asbestos exposure produces asbestosis.

Both chrysotile and the amphiboles appear to have similar fibrogenic potential although that of the latter may be more severe. The contribution of smoking to the fibrosis is unclear, with some studies purporting to show a higher prevalence of interstitial disease among asbestos-exposed smokers (63–66) and others finding no such association (67–69).

Because of the demonstration of consistent exposure-response curves, coupled with the observation of fewer and milder cases of fibrosis in workers exposed to the lower dust levels of more recent times, it is believed that strict observation of current permissible exposure limits, engineering and safety controls, and good workplace practices should make the appearance of future cases of asbestosis extremely rare (58).

Macroscopic examination of the asbestotic lung reveals that the fibrosis almost always begins in the subpleural areas of the lower lobes and extends upward as its severity increases. Patchy involvement is common. The hallmark of microscopic diagnosis is the simultaneous presence of both fibrosis and asbestos bodies. In advanced asbestosis cases, areas of honeycombing may appear in the affected lung areas.

The most common presenting symptom in the patient with asbestosis is dyspnea. Rales—characteristically bilateral, pan- or end-inspiratory, and best heard laterally or posteriorly—are present on physical examination in over 50% of patients, but are not specific. Clubbing is less common, nonspecific, and generally appears late in the course of the disease.

Pulmonary function studies, when abnormal, typically reveal a restrictive lung pattern, with a reduction in vital and total lung capacities, and preservation of the FEV₁/FVC ratio. Lung diffusing capacity, although variable, may also be low, and relative hypoxemia can be present in advanced stages of the disease.

The radiologic appearance of asbestosis is characterized by the presence of bilateral small, irregular interstitial opacities beginning in the lower lobes. The concentration or “profusion” of these opacities increases with the severity of the disease and correlates roughly with both cumulative exposure (63) and a reduction in lung volumes (46,70), particularly at higher grades of profusion. A gradient for profusion has been quantitated by the International Labour Office (ILO) (71), but interpretation of mini-

mal degrees of profusion can be particularly difficult. Several factors contribute to this. First of all, interobserver variability is present in interpretation of radiographic changes, even when the standards set out by the 1980 ILO Classification of Radiographs of the Pneumoconioses are used. Second, the positive predictive value of mild increases in interstitial markings for asbestosis is low, and other factors should be entertained in the differential diagnosis. Some studies have found interstitial markings to be more prevalent among smokers and, indeed, in some cases, to regress at least partially after cessation of asbestos exposure and smoking (72). Lung function is generally normal or minimally impaired at this stage of disease. On the other hand, longitudinal studies have suggested a progression of profusion in those who develop asbestosis, if the disease worsens (73). Unfortunately, physicians are frequently asked to make a judgment at a single point in time, which often is the case when evaluating compensation cases. While there would be little uncertainty in the case of a symptomatic asbestos worker who presents with rales, clubbing, a restrictive lung defect, and a chest radiograph showing bilateral calcified pleural plaques and advanced interstitial fibrosis, the majority of cases are not as straightforward. Recently, the American Thoracic Society and the American College of Chest Physicians both recognized that characteristic radiographic changes, coupled with an adequate history of exposure, may be sufficient to establish a diagnosis of asbestosis (58). The additional presence of rales, clubbing, lung restriction, or a low diffusing capacity increases the certainty of the diagnosis. It is generally accepted that, in the presence of a history of occupational asbestos exposure and compatible clinical-radiological findings, the benefit of the doubt weighs in favor of a diagnosis of asbestosis (58). Lung biopsy is not necessarily obtained for diagnosis. When performed, however, tissue obtained by open lung biopsy is preferable to transbronchial biopsy because of the low yield of adequate tissue and nonspecificity of the latter technique (27). Guidelines for the pathologic diagnosis of asbestosis have been published jointly by the College of American Pathologists and NIOSH (74).

OBSTRUCTIVE AIRWAYS DISEASE

There exists some controversy as to whether chronic inhalation of asbestos fibers can also induce obstructive airways disease. Examination of the lungs of asbestos-exposed animals and humans has shown that the earliest injury occurs at the level of the respiratory bronchiole (75,76). Likewise, some epidemiologic studies have reported lower mid-expiratory flow (MMF) rates, decreased flows at low lung volumes, and diminished closing volume (CV) values among asbestos workers, suggestive of “small

airways disease" (77-79). This difference persisted after adjusting for smoking history in those studies where this was considered. However, MMF, CV, and decreased flows at low volumes are fraught with a great deal of variability (80) and are of uncertain long-term significance. Furthermore, dose-response relationships between exposure levels and degree of airflow abnormality have been difficult to document. A higher prevalence of clinically significant airway obstruction, as reflected by decreases in the FEV1/FVC beyond that attributable to smoking alone, has not been consistently observed in asbestos-exposed individuals (77,81). In general, obstructive lung defects in these populations appear to be the result of the high prevalence of smoking.

Asbestos-associated malignancy LUNG CANCER

Studies of asbestos-exposed workers have consistently demonstrated an excess number of lung cancer deaths (82-86). This risk is further increased among smokers, above that expected from a simple additive effect of both exposure and smoking (42). Occupational studies have shown a linear relationship between cumulative asbestos exposure and lung cancer mortality (23). At low levels of exposure, however, it is unclear whether a threshold exists below which there is no excess risk. This question is of considerable importance, particularly with respect to consequences of environmental exposure to asbestos. Due to the lack of data on exposure at these low levels, risk estimation studies (4,23,25) have in general assumed a linear no-threshold model for purposes of recommending standards, extrapolating from health effects at higher, generally occupational, exposures. The rationale underlying this assumption presumes a "worst possible" situation on which to base subsequent risk estimates.

Some uncertainty exists as to whether asbestos is a complete carcinogen (ie, able to initiate carcinogenesis by itself), or if it acts as a tumor promoter or cocarcinogen, at least in the case of lung cancer (4). Proponents of the latter point to several observations (87,88). First, the excess number of lung cancer cases among asbestos-exposed nonsmokers (in those studies where these data are available) occurs predominantly among workers with concomitant evidence of asbestosis (8). Second, there is some evidence that the incidence of lung cancer in individuals with other fibrotic lung diseases (eg, idiopathic pulmonary fibrosis, pulmonary systemic sclerosis) is increased, suggesting that the fibrosis itself may be associated with subsequent malignancy (87). Some authors have noted that lung cancer in these patients preferentially arises in the lower lobes as does the fibrosis, unlike the usual situation of upper lobe predominance of bronchogenic tu-

mors (88). In the United Kingdom, bronchogenic carcinoma is attributed to asbestos only if there is also concomitant evidence of asbestosis. Laboratory studies of mutagenicity and carcinogenicity have produced somewhat conflicting results. Whereas a few studies have reported a weak mutagenic effect of asbestos in certain cell lines (89), most have failed to observe this (4,90). Animal studies of asbestos and carcinogenicity favor the role of asbestos as a tumor promoter or cocarcinogen, at least in the case of lung cancer (4).

Most cases of bronchogenic carcinoma in asbestos-exposed individuals appear after a latency period of 20 years or more. While not all fiber types show the same risks, there does not appear to be a predominant fiber type responsible for the observed excess lung cancer rates (91). Likewise, there is no firm evidence of a predominant histologic type of bronchogenic carcinoma in asbestos-exposed populations (92), although earlier a slight predominance of adenocarcinoma was reported by some authors (93).

MESOTHELIOMA

There is little question as to the causal association between asbestos exposure and the occurrence of malignant mesothelioma. Several observations support this relationship. Mesothelioma is rare in the nonexposed population, although cases have been reported (94-96). Epidemiologic studies have consistently identified cases in asbestos-exposed groups, regardless of occupational setting (4,16,94). Clusters of mesothelioma cases among relatives of asbestos workers and individuals living near asbestos plants have been described as well (19-21,94). Also, mesotheliomas have been produced in animal studies following inoculation and/or inhalation of asbestos (97,98). Finally, an exposure-response relationship has been reported between years elapsed since onset of exposure and appearance of these tumors, although based on relatively few studies (99). This exposure-response curve appears to be exponential, not linear, with most cases appearing after a latency period of 30 or more years (23). There is evidence supporting the existence of a differential risk gradient according to fiber type, with crocidolite posing the greatest hazard (23). Smoking does not appear to increase the risk of mesothelioma among asbestos-exposed subjects. As is the case with bronchogenic carcinoma, there is some debate (100) as to whether a threshold exists below which no excess mesothelioma deaths would be expected to occur, although risk estimates also are based on a no-threshold model (4,23,24). There are data, however, on mesothelioma cases appearing several years after relatively brief and probably lower exposures than those observed in the other asbestos-associated diseases (101).

The most common presenting symptoms of the patient with mesothelioma are unremitting chest pain and increasing dyspnea upon exertion. Chest radiographs may show a moderate or large effusion and pleural thickening encroaching on the interlobar fissures and infiltration of the mediastinum, as the tumor progressively encases the lung and neighboring structures. Establishing a pathologic diagnosis prior to death is frequently difficult. Closed-needle biopsy of the pleura and pleural fluid analysis may have a low diagnostic yield; open- or thoracoscopically-guided pleural biopsy procedures produce better samples. Other tumors such as metastatic adenocarcinoma may mimic mesothelioma, and frequently a combination of gross pathology, microscopic study of specimens, and histochemical testing for the presence or absence of certain mucins and enzymes is required for a definitive diagnosis.

OTHER MALIGNANCIES

Although there is general agreement on the association between asbestos and both lung cancer and mesothelioma, a consensus does not exist as to whether there is an increased risk of other tumors such as gastrointestinal, laryngeal, renal, and ovarian carcinomas in asbestos-exposed populations. Among these tumors, the epidemiologic evidence is most abundant for tumors of the digestive tract, with some studies reporting an increased risk, although not always statistically significant, among those exposed to asbestos (85,102,103); other studies have not found such an increase (29,104). Exposure-response relationships have not been documented in studies of asbestos exposure and tumors of non-respiratory sites, the biological plausibility of an effect has been questioned, and animal experiments have been unable to substantiate the association of gastrointestinal tumors with asbestos exposure (4,105). Doll and Peto (106) suggest that misclassification of cases of peritoneal mesothelioma as gastrointestinal cancer may account for most of the observed excess. Notwithstanding this, OSHA considered gastrointestinal cancer as probably associated with asbestos exposure when it recently revised its exposure limits (16).

There are fewer data on the associations between tumors other than gastrointestinal and lung and asbestos exposure. Although some studies have suggested an excess number of laryngeal carcinoma cases among asbestos workers, these studies were limited by problems with study design, lack of adequate reference populations, and lack of adjustment for the confounding effects of smoking and alcohol intake (4,107). Even so, the likelihood of misdiagnosis of laryngeal carcinoma, particularly in case-control studies, is low, and an argument is made for the biological plausibility of such an association.

This association, therefore, remains unresolved and further study seems warranted (106).

Role of the primary physician

The primary physician has two important roles with respect to patients with a history of asbestos exposure: the identification and counseling of individuals at risk and the accurate diagnosis of asbestos-associated diseases when present. Obtaining a careful occupational history, which includes a detailed description of onset of exposure and the duration and nature of exposures, cannot be overemphasized. Likewise, an accurate smoking history and careful review of radiographs for evidence of both malignant and nonmalignant pathology are essential. When identified, persons at risk should be accurately informed as to possible complications deriving from their exposure and the health significance of any pulmonary changes. Baseline and periodic pulmonary function testing, as well as radiographs, may be helpful in this assessment. When a possible asbestos-associated disease is identified, the patient should be informed, for purposes of compensation, of the existence of a statute of limitations from the date of notification.

If a diagnosis of asbestosis is suspected or confirmed, the case should be reported either to the local health authority or directly to the Epidemiology Division, Texas Department of Health. Reports are accepted by mail or toll-free telephone report (1-800-252-8239). These rules provide for strict confidential handling of case reports. To better serve the purposes of surveillance, a precise case definition for asbestosis has not been established. However, the epidemiologic surveillance criteria for a case is stated as "a person in whom an occupational disease is diagnosed by a physician based upon clinical evaluation, interpretation of laboratory and/or roentgenographic findings, and an appropriate occupational history" (108). Pleural plaques do not require reporting. Mesothelioma, as well as any other cancer, is reportable under the Texas Cancer Control Act.

OSHA requires that a preplacement medical examination be performed prior to assigning an individual to a job with potential for exposure to airborne asbestos. For active employees, an annual comprehensive medical examination is required. Chest roentgenographs should be offered "at 5 year intervals during the 10 years following any employee's first exposure to asbestos. After 10 years from the employee's first exposure, the age category of an employee will determine the frequency of x-ray testing: up until age 35, x-rays will be required at 5 year intervals; between the ages of 35-45 medical examinations will be required every 2 years; and above age 45, x-ray will be required on an annual basis" (16).

Compliance with current exposure control measures, coupled with ongoing surveillance, scientifically sound policy decisions, and heightened worker awareness should make the asbestos-associated diseases virtually obsolete in the near future.

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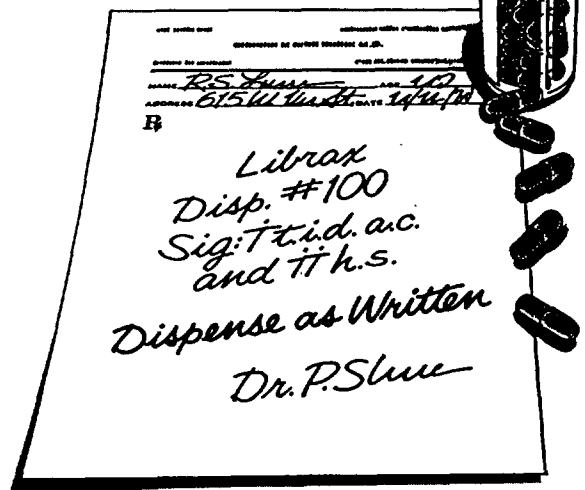
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Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur. Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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