Pulm

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MEDICAL GRAND ROUNDS
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ASBESTOS-RELATED PULMONARY DISEASES

When a doctor visits a working class home, he should be content to sit on a three-legged stool if there isn't a gilded chair, and he should take time for his examination; and to the questions recommended by Hippocrates, he should add one more - What is your occupation?

Bernardino Ramazzini, 1713

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INTRODUCTION

Asbestos is one of our most useful minerals. Over 3,000 manufactured products of contemporary importance contain this mineral. Asbestos is employed in construction material because it is resistant to thermal and corrosive destruction and increases the tensile strength of the product. These properties are also the basis for the use of the mineral in friction equipment and in a wide variety of consumer items requiring relatively inexpensive insulation material that is light and subject to molding. Since the turn of the century about 3×10^7 tons of asbestos have been used in construction and in fabrication of manufactured goods in the United States. At present, several million Americans are employed in industries that use asbestos products and countless millions of Americans are exposed to asbestos cryptically in the course of their daily lives. Public concern over the effects of asbestos on health is mounting. This unprecedented interest has extended well beyond the medical, public health and biomedical research professionals, and there is no health issue which has had as much potential for interaction between social scientists, research investigators, government officials, industrial management, labor organizations and members of the legal profession. Litigation based on personal injury consequent to pulmonary fibrosis and cancer is an increasing problem for companies involved in the manufacture, use and distribution of asbestos. The magnitude of this public problem can be appreciated from the fact that 16,000 law suits relating to asbestos-induced disease are currently pending in the Manville Corporation alone (1). The spectrum of liability has now widened to involve the federal government for alleged negligence in establishing adequate environmental standards.

While environmental controls have been enacted, it is likely that asbestos related diseases will continue to increase in incidence and prevalence during the 1980's and will assume an even greater role in the daily practice of medicine. Thus, the purpose of this discussion will be to summarize the current knowledge of the epidemiology, pathophysiology and clinical features of asbestos-related diseases.

HISTORICAL BACKGROUND

The unique usefulness of asbestos has been recognized since antiquity. Ancient man incorporated it into pottery 4500 years ago (2). The ancient Greeks found that asbestos could be woven into cloth used for cremation shrouds and for the wicks of the eternal lamps of the Vestal Virgins (3). While reference to this remarkable mineral can be found throughout history, the commercial exploitation of asbestos was minimal until modern times. The Industrial Revolution was powered by the steam engine and the need for insulation of these engines dramatically increased the use of asbestos in the late nineteenth century (4). At this time, asbestos was first used in the United States in the manufacture of roofing materials and cement. During and after the Second World War, production of asbestos increased at a phenomenal rate (5). Between 1970 and 1975, asbestos consumption in the United States averaged approximately 800,000 tons annually. The United States Bureau of Mines estimates that the demand for asbestos in the United States in the year 2000 will be approximately 1.8 million tons (6).

Adverse health effects of asbestos were recognized even in ancient times. Pliny the Younger (61-114 A.D.) noted a sickness in the lungs of slaves weaving asbestos cloth (3). It is unlikely that asbestosis was recognized as a disease before the term pneumonkoniosis was introduced by Zinker in 1867. Sporadic reports of disease associated with asbestos began to appear in the medical literature during the early years of this century, and the term asbestosis was introduced in 1924 (7). By the 1920's and 1930's the disease was more commonly recognized and series of cases appeared in the literature. In the 1930's, the technique of spraying asbestos insulation in construction was developed, and shortly thereafter asbestos began to be used in the manufacture of insulation and pipe.

The occurrence of bronchogenic carcinoma in a patient with asbestosis was reported in 1935 and this observation was quickly confirmed (8). Although worldwide concern about the health affects of asbestos mounted at this time the problem became more critical during the mobilization that accompanied World War II. Warfare demanded ships and modern weaponry and the war effort brought thousands of persons into industries that used asbestos.

Tumors known by the designation mesothelioma were described in 1931 (9) but recognition of the association of the neoplasm with asbestos awaited reports in the 1950's (10, 11). In 1960, the common occurrence of this rare neoplasm in persons exposed to South African Cape blue asbestos was noted (12). Subsequent experiments documented the induction of morphologically similar pleural lesions in animals after the interpleural introduction of asbestos (13).

In summary, asbestos exposure is associated with a wide variety of diseases as shown in Table 1 including, 1) asbestosis (diffuse interstitial pulmonary fibrosis), 2) benign pleural effusions, 3) parietal pleural plaques, 4) bronchogenic carcinoma, and 5) diffuse malignant mesothelioma of the pleura.

Table 1

Asbestos Related Pulmonary Diseases

Asbestosis
Benign pleural effusion
Parietal pleural plaques
Bronchogenic carcinoma
Diffuse malignant mesothelioma

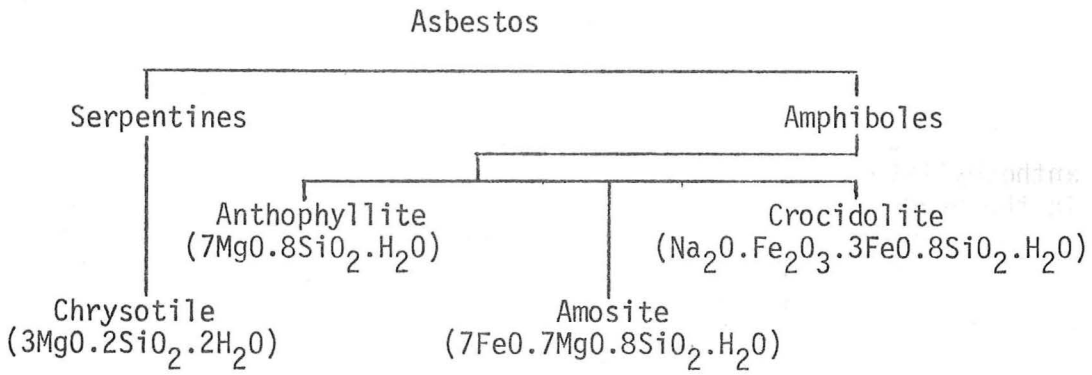
MINERALOGY

Asbestos is not one mineral but a family of hydrated silicates that have a fibrous morphology defined as a length to width ratio greater than 3:1. The term asbestos refers to the commercial product after mining and processing

and is not a mineralogical designation. Governmental agencies and industrial organizations restrict the term asbestos to those fibrous silicates in the group that are commercially exploitable. Two main subgroups are recognized: serpentine and amphibole. The most important of these fibrous silicates are the serpentine mineral chrysotile, and the amphibole minerals crocidolite, amosite and anthophyllite (Figure 1).

Figure 1

Types of Asbestos of Commercial and Medical Importance and Their Chemical Compositions



Craighead, N. Eng. J. Med. 306:1446, 1982

Chrysotile (white asbestos) is a serpentine asbestos that accounts for approximately 95 percent of the asbestos used worldwide. It is composed of pliable, curly fibers made up of bundles of smaller fibrils. Its fibers are the most slender, natural fibers known (about 1/1000th the diameter of a human hair). The subunits are composed of either multi- or single layers of silica and brucite (MgO) that form concentric scroll-like tubes. In neutral aqueous media, the brucite is ionized and gives the fiber a positive charge. Chrysotile is mined chiefly in Canada and the USSR. The different members of the amphibole family are distinguished from each other by the hydrated cations found between the silica layers. Crocidolite (blue asbestos), amosite (brown asbestos) and anthophyllite fibers vary in diameter depending on the degree of separation achieved in processing. Crocidolite tends to form thinner fibers than amosite and amosite thinner fibers than anthophyllite. There is an impression that crocidolite is more fibrogenic and carcinogenic than other forms of asbestos and this has led to efforts to curtail its application. Crocidolite is mined predominantly in the Cape region of South Africa. Amosite is mined principally from the Transvaal while Finland is the main source of anthophyllite.

The chemistry of asbestos is complex. A number of trace metals, including Ni, Fe, Sb, Cr and Co are associated with native chrysotile and crocidolite. These elements can be leached from the fibers after treatment with inorganic and organic acids. Crocidolite is acid stable whereas chrysotile is more

acid labile. Both fibers can undergo chemical alteration in the lung. Both types of asbestos are heat resistant and possess great tensile strength which accounts for their desirability for the many industrial uses of asbestos. Both types of fibers appear to be coated *in vivo* with pulmonary micromolecules such as lung surfactant.

ASBESTOSIS

Epidemiology

Increased prevalence of radiologic signs of asbestosis or pulmonary function impairment have been found in surveys of asbestos workers in a variety of occupational settings. All studies having long term follow-up have shown increased death rates from asbestosis (14). Radiologic changes consistent with asbestosis have been demonstrated in household contacts of asbestos factory workers (15).

Exposure to all forms of asbestos is capable of producing pulmonary fibrosis. Crocidolite appears to be the most potent followed by amosite, anthophyllite and chrysotile (5, 16). There is a dose-effect relationship in the production of fibrosis related to increasing total dose. Small exposures over many years have the same impact as a brief, intense exposure. There may exist a "safe threshold" for asbestos exposure below which lung fibrosis does not occur (17). However other studies have not supported this concept and have pointed out limitations in cumulative dose as a measure of exposure (18, 19).

Smoking is a very common habit among asbestos workers and it has been difficult to evaluate its effect. Prospective cohort studies suggest that smoking increases mortality from asbestosis (20). Other studies indicate that the prevalence of radiographically visible pleural and parenchymal changes is higher in smoking asbestos workers than in those who do not smoke (21-23). Selikof has concluded that the risk of dying from asbestosis is 2.6 times higher in smokers than in non-smokers (24).

Clinical Presentation

The clinical findings in asbestosis are basically those of any diffuse infiltrative lung disease (3, 5, 16, 25-29). The most common symptom associated with asbestosis is shortness of breath. This symptom first occurs with the stress of moderate to severe exercise. As asbestosis progresses minimal exertion elicits dyspnea and in its most severe state, the disease causes shortness of breath even at rest. Dyspnea related to asbestosis may be seen as early as 10 years after the onset of exposure, but more commonly takes 20 years or more to appear (16). Cough is also present in most instances and may be severe, paroxysmal and distressing. Paroxysmal cough often occurs in relation to effort and appears to be associated with the presence of small amounts of particularly viscous sputum. In the majority of cases the volume of sputum is small and usually nonpurulent. Hemoptysis does not occur in the absence of complicating carcinoma or unrelated lung disease. Chest discomfort, often described as an ache which apparently arises in intercostal and other chest wall muscles, is present in approximately one-third of individuals and is usually accompanied by severe dyspnea. Fatigue, chest tightness and inability to breathe are occasionally seen in advanced disease.

Table 2

Presenting Symptoms of Asbestosis

Symptom	Percent of Patients
Dyspnea	92
Cough	81
Sputum production	50
Chest discomfort	30
Fatigue	10

Hunter, Diseases of Occupations, page 877, 1955
Wyers, Postgrad. Med. J. 25:631, 1949
Thomson, Clin. Sci. 21:1, 1961
Smither, Ann. N.Y. Acad. Sci. 132:166, 1965

The physical signs of asbestosis are also nonspecific (3, 5, 16, 25-29). Patients usually breathe with a rapid, shallow respiratory pattern. On pulmonary auscultation, fine, dry, "velcrolike" rales are heard in virtually all patients. These sounds are believed to reflect the opening of closed airways in lung regions involved with an interstitial process. In early asbestosis, rales are heard only at the lung bases at the end of maximal inspiration or following a voluntary cough. As the disease progresses, rales are heard throughout respiration. Large airway sounds or rhonchi are not heard and wheezing is not present in asbestosis. Clubbing of the fingers and toes is present in approximately three quarters of cases but does not correlate well with radiographic severity of disease. Rapid increase in clubbing may indicate the development of an associated bronchogenic carcinoma. Central cyanosis is rarely seen at rest but it may develop after exercise. Friction rubs are also heard in rare individuals.

Table 3

Presenting Signs in Asbestosis

Sign	Percent of Patients
Rales	96
Clubbing	77
Cyanosis	4
Friction rub	3

Hunter, Diseases of Occupations, page 877, 1955
Wyers, Postgrad. Med. J. 25:631, 1949
Thomson, Clin. Sci. 21:1, 1961
Smither, Ann. N.Y. Acad. Sci. 132:166, 1965

Asbestosis is associated with abnormalities of the immune system (30-32), however, none of the abnormalities are specific for this disorder. The most commonly noted abnormality is an abnormal pattern of serum protein electrophoresis. Elevations in alpha-2, beta and gamma globulins have been noted. Elevated sedimentation rates have been noted in approximately one-third of individuals. Approximately one-third of patients with asbestosis manifest hyperactivity of their humoral immune system. Antinuclear antibodies and rheumatoid factors are found in approximately one-third of individuals. Elevations in serum immunoglobulins and increased prevalence of non-organ and organ-specific autoantibodies have also been described.

Table 4

Immunologic Abnormalities in Asbestosis

Study	Percent of Patients
Abnormal protein electrophoresis	62
Antinuclear antibodies	28
Rheumatoid factor	27
Elevated serum immunoglobulin	31
Autoimmune diseases	?
Tumors of B-cell origin	?

Turner-Warwick, Brit. Med. J. 3:492, 1970
Williams, Thorax 15:109, 1960
Doll, Clin. Chest Med. 4:3, 1983

Collectively, these observations support the concept of B cell hyperactivity in asbestosis. Further evidence for B cell hyperactivity is provided by the association between asbestosis and autoimmune diseases. Both rheumatoid arthritis (33) and systemic lupus erythematosus (34) have been reported with increased frequency in patients with asbestosis. Additionally, tumors of B cell origin (multiple myeloma, chronic lymphocytic leukemia, lymphoma and Waldenstrom's macroglobulinema) have been observed with increased frequency in asbestosis populations (34-37). Depression of T suppressor cell function could allow B cell hyperactivity with the result being production of autoantibodies, immunoglobulins and immune complexes. It is interesting that recent studies have shown defective T suppressor activity in patients with asbestosis (38).

Radiographic Findings

TThe radiographic appearance of asbestosis is characterized by linear, irregular opacities principally in the lower lobes (39-43). The International Labor Office International Classification of radiographs of the pneumoconioses has recognized three subsets of irregular opacities designated "s", "t" and "u". The "s" opacities have widths of up to 1.5 mm. The "t" opacities have widths of 1.5 to 3 mm. The "u" opacities range in width from more than 3 to less than 10 mm and carry the poorest prognosis for survival of the 3 subsets.

In addition to the appearance of the individual opacities, their concentration and extent are obviously important. The type, concentration and extent of these opacities correlate reasonably well with changes in pulmonary function. Rounded opacities similar to those of silicosis and coal workers' pneumoconiosis are occasionally seen (44) and in many cases, are probably secondary to silicosis and not asbestosis. Free silica is often present in asbestos processes in the United States. Rarely, larger opacities resembling those of Caplan's syndrome are present in patients with rheumatoid disease (45). Large opacities like those of progressive massive fibrosis of coal workers' pneumoconiosis may be encountered in asbestos miners and millers. These large opacities usually occur in the lower lobes, and probably result from mixed exposure to dust containing both silica and asbestos. Combinations of visceral pleural and parenchymal disease may create a hazy, "ground glass" appearance over the lower lung field or might obscure the heart border ("shaggy heart") and the diaphragm if severe. Pleural changes are present in more than 50 percent of cases of asbestosis (40). Kerley B-lines are often times seen. These are short, horizontal lines observed in the periphery of the lower lung field and are believed to represent lymphatic obstruction (46). In advanced parenchymal disease, emphysematous changes and honeycomb cysts may be observed. The honeycombing tends to further obscure the cardiac and diaphragmatic contours.

Table 5

Radiographic Characteristics of Asbestosis

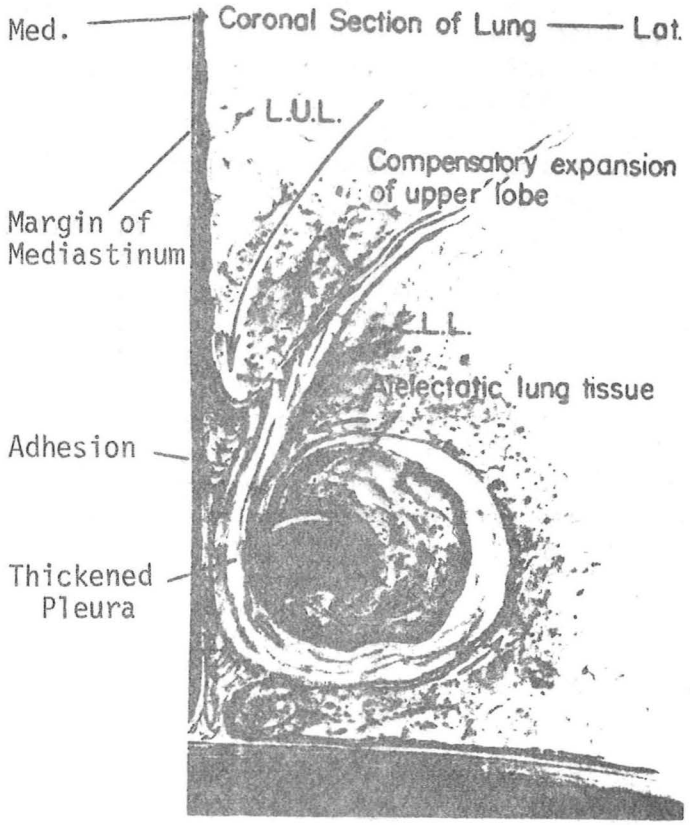
Irregular and/or round opacities
Ground-glass appearance
Kerley B-lines
Hair-like ring (honeycomb) shadows
Pseudotumor

There is an unusual radiographic manifestation of asbestosis known as a pseudotumor (47, 48). This phenomenon is produced by infolding of asbestotic atelectatic pulmonary parenchyma underlying localized fibrotic thickening of the visceral pleura.

Pseudotumors tend to develop rather abruptly in the periphery of the lower lobes. Their location and configuration are the best clues to their benign nature.

Figure 2

Rounded Atelectasis



Schneider, A. J. R. 134:231, 1980

Computed axial tomography is twice as sensitive as standard roentgenograms in detecting interstitial lung disease (49). In spite of this sensitivity the procedure also has disadvantages. The procedure is more complex, time-consuming and expensive than conventional chest radiography and involves considerable more radiation exposure. Thus, at the present time CAT should not be applied as a routine or screening procedure, but should be reserved for evaluating individuals with apparently negative standard chest radiographs but with altered pulmonary function and a history of exposure to asbestos.

Pulmonary Function Tests

Well established asbestosis is characterized by restriction of lung volumes and decreased compliance. Vital capacity and total lung capacity are reduced below values predicted according to the height of the patient. The functional residual capacity and the residual volume are also reduced below predicted values but not usually to the same extent as the vital capacity so that the ratio of residual volume to total lung capacity is usually elevated.

However, instead of indicating hyperinflation or emphysematous changes in the lung, the high RV to TLC ratio in this group of disorders reflects severe restriction of the vital capacity. Airflow measured by the FEV_1 is decreased in proportion to volume restriction indicating the absence of airways obstruction (26-29, 32).

Table 6

Pulmonary Physiologic Studies in Asbestosis-Ventilation

Study	Mean Percent Predicted
Vital capacity	65
Total lung capacity	64
Residual volume/total lung capacity	115
Forced expiratory volume - 1 sec	100

Smither, Ann. N. Y. Acad. Sci. 132:166, 1965
Thomson, Clin. Sci. 21:1, 1961
Williams, Thorax 15:109, 1960

Gas exchange capabilities are usually impaired in asbestosis, reflected by arterial hypoxemia, and increased alveolar-arterial PO_2 gradient, and hyperventilation (32, 50, 51). These abnormalities may first be evident only under the stress of exercise but later occur at rest. CO_2 exchange is not usually affected and arterial CO_2 retention is not a feature of the established disease. Diffusing capacity of the lung is also decreased in asbestosis contributable in part to the decreased lung volume although decreased membrane transfer and inhomogeneity of regional ventilation perfusion relationships within the lung undoubtedly contribute to the impaired diffusion capacity.

Table 7

Pulmonary Physiologic Studies in Asbestosis Gas Exchange

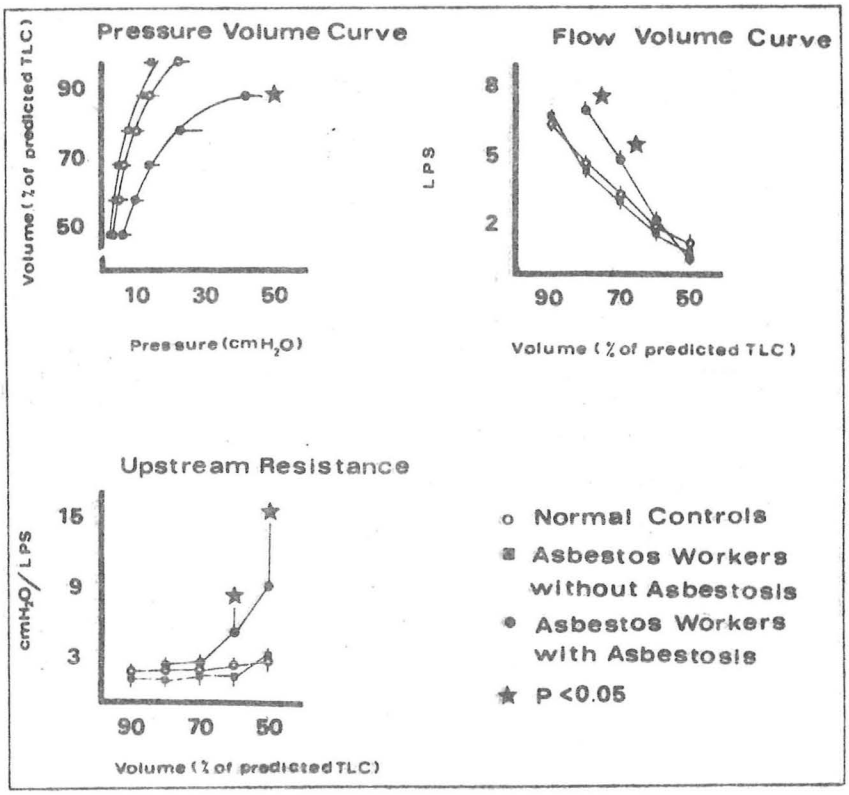
Study	Mean Value	
PaO_2	85	mm Hg
(A-a) O_2	23	mm Hg
Shunt	10	%
V_D/V_T	46	%
Diffusing capacity	11.2	ml/min/torr

Bjure, Thorax 19:22, 1964
Leathart, Brit. J. Ind. Med. 17:213, 1960
Williams, Thorax 15:109, 1960

Whether occupational exposure to asbestos plays a role in the development of airways disease is a controversial clinical issue. Epidemiologic surveys (52, 53) have shown an increased prelevance of bronchitic symptoms in relation to asbestos exposure, which would be consistent with the concept of industrial bronchitis. Furthermore, several studies of airway function in asbestos workers (54-56) have found an increased incidence of obstructive patterns of lung function, but these reports were largely based on populations of cigarette smokers. When the effects of smoking habit were taken into account and the selection of control populations with smoking histories similar to those of the asbestos workers surveyed, air flow limitation was not excessive in a population exposed to low levels of asbestos (57). A recent study of non-smoking older asbestos workers documented three to four fold increases in upstream airway resistance at low lung volumes consistent with peripheral airway obstruction (58). In none of the cases, however, was this airway obstruction severe enough to reduce significantly the usual spirometric parameters of airway obstruction, and in none of these men did it cause a significant reduction in the ratio of forced expiratory volume in one second to forced vital capacity. Thus, while small airway obstruction appears to result from asbestos exposure, it is unlikely that it accounts for the mild obstructive pattern of pulmonary function often observed on flow volume curves in cigarette smokers with the disease. Whether asbestos exposure has an additive or synergistic effect with smoking in regards to bronchitic symptoms remains to be clarified.

Figure 3

Airways Disease Following Asbestos Exposure



Begin, Am. J. Med. 75:635, 1983

Criteria for Diagnosis of Asbestosis

The criteria for diagnosis of asbestosis depend on the purpose for which the diagnosis will be used and the degree of certainty required. Parkes has established the criteria shown in Table 8 for diagnosis of asbestosis (16). If the first four criteria are present the diagnosis would generally be considered established by most compensation boards. With fewer criteria, there is less certainty.

Table 8

Criteria for Diagnosis of Asbestosis

History of occupational exposure to asbestos

Persistent bilateral rales with or without finger clubbing

Radiographic evidence of diffuse interstitial fibrosis in the lower half of the lung. Bilateral pleural plaques provide corraborative evidence

Impairment of lung function

Dyspnea on effort

Asbestos bodies in sputum

Parkes, Brit. J. Dis. Chest 67:261, 1973

If four or more of these criteria are present, a lung biopsy is seldom warranted. However, in the absence of an exposure history or if the exposure history is considered too short to account for the amount of disease present or in contested compensation cases, tissue diagnosis may be necessary. If a biopsy is performed, open biopsy is the procedure of choice. Transbronchial biopsy is generally inadequate to make the diagnosis of asbestosis. An open lung biopsy is the most likely to be successful especially in mild disease (59).

Pathology

The histopathologic diagnosis of asbestosis requires 2 features: 1) diffuse interstitial fibrosis, and 2) the presence of asbestos bodies in lung tissue sections (60). In animal studies, early asbestos reactions are characterized by an accumulation of inflammatory and immune effector cells (alveolitis) (61), a reaction which resembles desquamative alveolar responses in man (46). Patients with desquamative interstitial pneumonia with asbestos bodies in the lungs have been reported (62, 63), and this probably represents the earliest lesion of asbestos exposure. The early reaction in the interstitial tissue

resembles that of other forms of interstitial pneumonia, with mixed leukocyte infiltration of the alveolar walls, moderate numbers of phagocytes in the alveoli, and varying degrees of organization with fibrosis (64). In many instances, the early changes are concentrated at the level of the respiratory bronchiole, where reticulin fibers, macrophages and dust particles collect leading to the basic lesion of asbestosis, namely a peribronchiolar fibrosis (65). The process then extends outward to involve the surrounding alveoli, leading to diffuse alveolar wall thickening, with peribronchiolar and perivascular fibrosis. In an occasional case, the fibrosis remains almost exclusively peribronchiolar, but the more usual picture is that of a diffuse fibrosis involving the interstitium, frequently associated with areas of solid fibrosis, where laminated collagen may replace the entire parenchyma. These areas may also show alveolar cell hyperplasia and sclerosis of vessel walls (65). As the disease progresses, the fibrotic pulmonary tissue contracts and is reorganized to form new air spaces typical of the honeycomb lung. It must be remembered that honeycomb lung is a common end stage of many types of fibrosing lung disease including asbestosis. Therefore, if tissue sections show only honeycombing in the absence of asbestos bodies, the diagnosis of asbestosis cannot be made on histopathologic grounds.

Asbestos bodies are required to make a tissue diagnosis of asbestosis (59, 60). The nature and significance of asbestos bodies and non-asbestos ferruginous bodies have been a source of controversy and confusion. Asbestos is inhaled as a bare mineral fiber. Once in the lung, a portion of these fibers are phagocytized by alveolar macrophages and coated with complexes of hemosiderin and glycoproteins. This process yields the familiar asbestos body, which appears as a transparent fiber encrusted with a golden yellow coat which may be sheath-like or segmented or knobbed. Asbestos bodies range in length from the lower limit of resolution to 70 μm or more and in thickness up to 25 μm.

The significance of asbestos bodies was initially questioned in 1963 when it was first reported that asbestos bodies could be found in a substantial fraction of an autopsied population who had no known exposure to asbestos (66). Subsequent reports from Western Europe and North America showed that asbestos bodies could be recovered from the lungs of virtually everyone in the population if suitable methods of digestion were employed (67). While urban air contains concentrations of asbestos fibers that are quite low, sufficient amounts of fibers are inhaled and deposited in the lungs of city dwellers to result in the almost universal demonstration of asbestos bodies at necropsy. These observations were the first evidence that the entire population was being exposed to asbestos.

This argument was countered by demonstrating that in experimental animals, similar appearing bodies could be formed on non-asbestos minerals such as fine fiber glass (68). On the basis of these experiments, it was concluded that the "ferruginous bodies" (a general term for mineral fibers of any sort with an iron protein coat) found in human lung from non-occupationally exposed individuals were not formed on asbestos. Recent work demonstrated clearly that this is incorrect. As a practical matter, most structures which resemble an asbestos body in fact contain asbestos, whether or not there is a history of exposure to this mineral (67). The one possible exception in humans is the formation of ferruginous bodies on erionite. These bodies are identical to asbestos bodies morphologically, but so far have only been

demonstrated in the population of a restricted area in Turkey (69). In the general population the core of these bodies is almost always amphibole asbestos; in workers with a history of exposure, bodies formed on chrysotile may also be found.

The fact that asbestos bodies can be recovered from every lung by techniques of digestion and concentration has led to concern about over diagnosing asbestosis in patients with interstitial fibrosis. However, recent studies have calculated that one should not observe an asbestos body in more than 1 in 100 sections from someone who has only background exposure to asbestosis (70). The implication of this calculation is that the observation of an asbestos body in a section of tissue is a reasonably good indication of some special (usually occupational) exposure to asbestos. The converse of this proposition is equally important. The finding of an asbestos body in histologic section implies only exposure. Asbestos bodies are not by themselves manifestation of disease, and especially, they are not adequate to make the diagnosis of asbestosis.

An equally controversial matter revolves around the question of whether cases of true asbestosis occur in which asbestos bodies cannot be found in tissue sections. A number of observations suggest that such a phenomenon could occur. It is known that asbestos fibers, the inhaled form of asbestos, form bodies in the lung with varying degrees of efficiency (71). In comparison to the various types of amphibole asbestos, chrysotile, the most commonly used kind of asbestos in North America, forms bodies poorly, probably because chrysotile fragments into very short fibers, which for unknown reasons do not form asbestos fibers. Additionally, cases of severe asbestosis with unequivocal histories of high level asbestos exposure may show very few bodies. In experimental animals, asbestos bodies go through a regular structural cycle which ends with the fragmentation of the body and it is possible that in some cases, all or most of the bodies that have formed have fragmented to the stage at which they are no longer identifiable (72). Finally, case reports exist of patients with diffuse fibrosis in whom no asbestos bodies were observed by light microscopy, but large numbers of chrysotile fibers were found in the tissue section by electron microscopy (73).

The number of uncoated fibers in the lung greatly exceeds the number of asbestos bodies in the tissue (67). It is not known why some fibers are coated and form the typical asbestos bodies, whereas others are uncoated. Since uncoated fibers are usually difficult or impossible to demonstrate by light microscopy lung tissue must be digested and the residue examined by either phase or electron microscopy in order to carry out qualitative and quantitative studies of the fibers. Whereas relatively long fibers (greater than 5 $m\mu$) are found by light microscopic techniques, electron microscopy makes it possible to identify very small particles. Thus far, attempts to correlate the extent of disease with either the number of asbestos bodies or the overall content of fibers in the lung have been difficult, although fibrosis is usually evident when 10^6 fibers per gram of lung are present.

Techniques are now available which allow quantitation of both asbestos bodies and fibers from pulmonary tissue and specific identification of the types of asbestos present. Quantitative studies pose many problems and are only a crude measure of exposure, partly because many fibers are cleared from the lung and others fragment to increasingly smaller particles with time. The techniques have largely been used for research purposes but do have some

application in regard to diagnosis and compensation for asbestos-induced injury. Several of these techniques are available in the Pathology Department at the University of Texas Health Science Center at Dallas. The uses for mineralogical analysis in the evaluation of asbestos-related disease are listed in Table 9.

Table 9

Mineralogic Diagnosis of Asbestos Induced Disease

Asbestos body count (light microscopy)

Use:

Quick screening test to rapidly confirm high asbestos burden

Advantages:

High value indicates definite exposure
Relatively inexpensive and quick to perform

Disadvantages:

Measures only a fraction of total asbestos load
Low count does not necessarily indicate lack of exposure
Yields no information about type of asbestos present

Examination of uncoated fibers (electron microscopy)

Use:

Measure total asbestos burden

Advantages:

Measures total number of fibers
Provides information on fiber type and size
May provide indication of source of exposure

Disadvantages:

Procedure is slow, expensive, and requires specialized equipment and extensive standards

Churg, Chest 83:275, 1983

Mineralogical analysis is useful in several circumstances. Quantitative studies allow documentation of exposure in the absence of either a good history or of asbestos bodies in histologic sections. Secondly, these studies allow documentation of the magnitude of exposure. Certainly, a stronger case can be made for asbestos causation of a given disease when a marked increase in fiber content is present. It is critical that a set of standard values documenting types, numbers, and sizes of fiber found in the background population be available from the laboratory which performs the analysis. The mere presence of asbestos in pulmonary tissue is, by itself, of no value. It

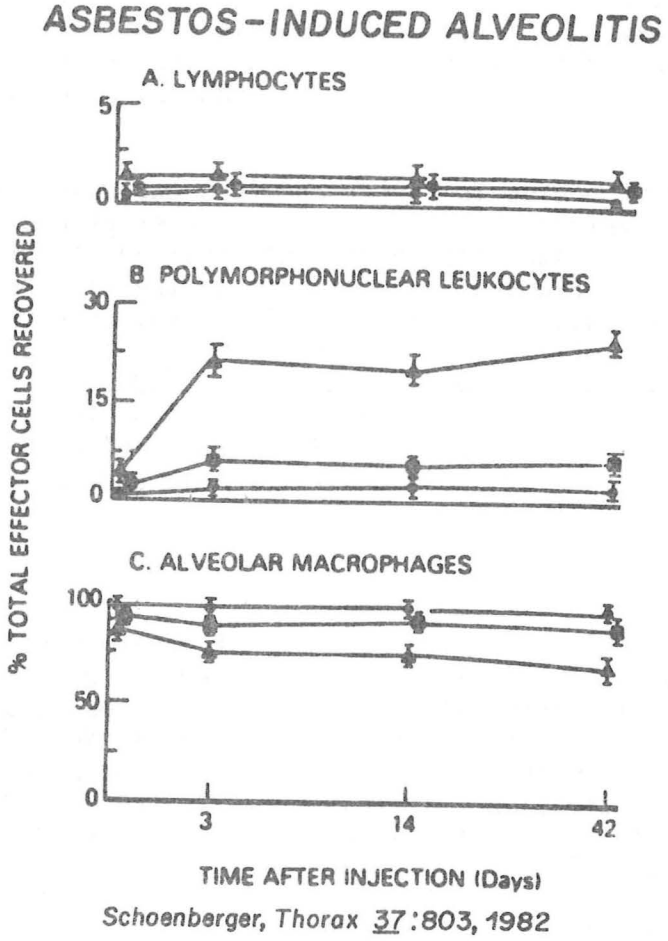
is important that not only numbers of fibers present, but the type of fiber be determined. For example, a lung containing a million fibers of chrysotile per gram of dry tissue is entirely consistent with a background exposure of the general population. A lung containing a million fibers of amosite or crocidolite per gram almost certainly indicates a fairly substantial occupational exposure to asbestos. At present, there are no set guidelines for determining what number of fibers may be etiologically associated with given diseases. Documentation of fiber type is useful in compensation cases when it is desired to demonstrate exposure to a specific product made by a certain manufacturer or used by a certain employer.

Quantitation of bodies is faster and less expensive than examination of fibers. When high values are obtained, the former procedure is useful for proving high pulmonary asbestos loads, but negative results do not entirely rule out such loads. Examination of fibers in the electron microscopy is slower and more expensive but gives definitive values both for numbers of fibers and for types of fibers. In any of these applications, only analysis of pulmonary tissue is of value. Tumor tissue and pleural plaques may or may not contain fibers or bodies and the few published studies in this area suggest that the relationship of fibers or bodies seen in plaques or tumors to the actual pulmonary concentration is quite variable and may not be at all representative (67).

Pathogenesis

Induction of alveolitis: For the majority of environmental agents causing lung disease, a general principal can be stated: the alterations of interstitial structure and function associated with these diseases results from an alveolitis, a state characterized by an expansion of the population of inflammatory and immune effector cells within the alveolar structures accompanied by a change in their state of activation. In this context, the first change to occur within the alveolar structures following inhalation of asbestos is an alveolitis. Following intratracheal injection of chrysotile asbestos fibers in guinea pigs, an intense neutrophil alveolitis is observed within three days (61). The relative proportions of inflammatory and immune effector cells present in bronchoalveolar lavage fluid are shown in Figure 4. At all time points, lymphocytes comprise two percent or less of bronchoalveolar cells in both asbestos injected and saline injected animals. By contrast, the percentage of bronchoalveolar cells that were polymorphonuclear leukocytes, including both neutrophils and eosinophils, was significantly greater in the asbestos injected animals than in the saline injected controls at all time points. The percentage of bronchoalveolar cells that were alveolar macrophages was significantly lower in the asbestos injected animals than in the saline injected control at all time points.

Figure 4



The effector cells that initiates the alveolitis following exposure to asbestos is the alveolar macrophage. The interaction between asbestos and alveolar macrophages results in "activation" of the macrophage (74, 75). The concept of macrophage activation as a distinct state remains controversial, because different agents seem to initiate different functional responses from a population of macrophages (76). For example, macrophages exposed to asbestos release both neutrophil chemotactic factor and a growth factor for fibroblasts, whereas macrophages exposed to cigarette smoke release only neutrophil chemotactic factor but not the growth factor (77, 78).

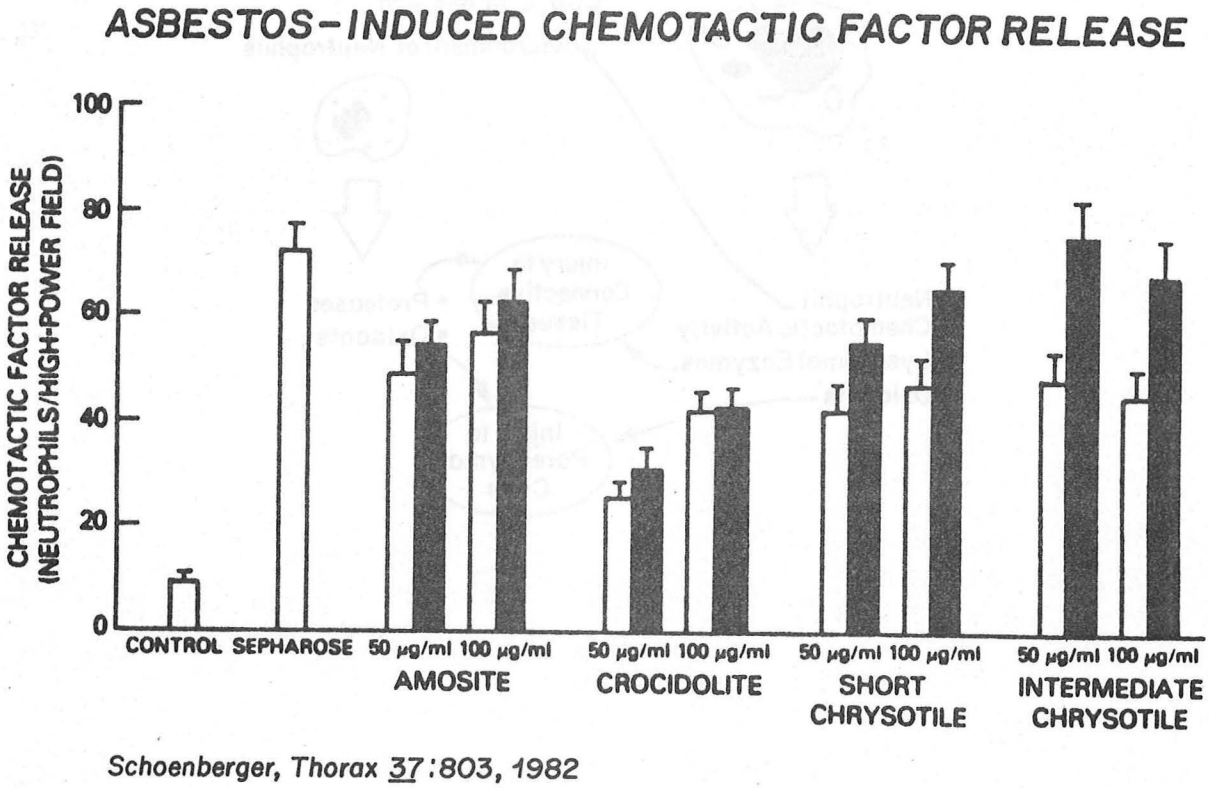
The state of macrophage activation induced by environmental agents lasts for a variable interval depending on the physical properties of the agent. Asbestos activation of an individual macrophage has been shown to persist for a long interval since asbestos is capable of macrophage activation without resulting in macrophage death. In contrast, silica activation of an individual macrophage probably lasts for a shorter interval since *in vitro* evidence

suggests that activation is followed by macrophage death in approximately two days (79). In summary, the central event in the generation of an alveolitis is believed to be macrophage activation, and it is the properties of the macrophage during the activated state that determines, to a large extent, the character of the alveolitis and thus the nature of the lung disease.

Macrophages activated by inhalation of asbestos can result in interstitial lung disease by production of a battery of inflammatory and immune products within the alveolar structures. While activated macrophages release many products, the macrophage functions that seem to be relevant to asbestosis include: 1) release of neutrophil chemotactic factor; 2) release of connective tissue specific proteases; and 3) release of oxidants.

There is increasing evidence that recruitment of neutrophils to the alveolar surface following exposure to asbestos is mediated by the alveolar macrophage by virtue of its ability to release a chemotactic factor for neutrophils. Exposure of normal guinea pig alveolar macrophages to each of four types of asbestos fibers, short chrysotile, intermediate chrysotile, amosite and crocidolite, resulted in significant release of neutrophil chemotactic factor by alveolar macrophages (Figure 5) (61).

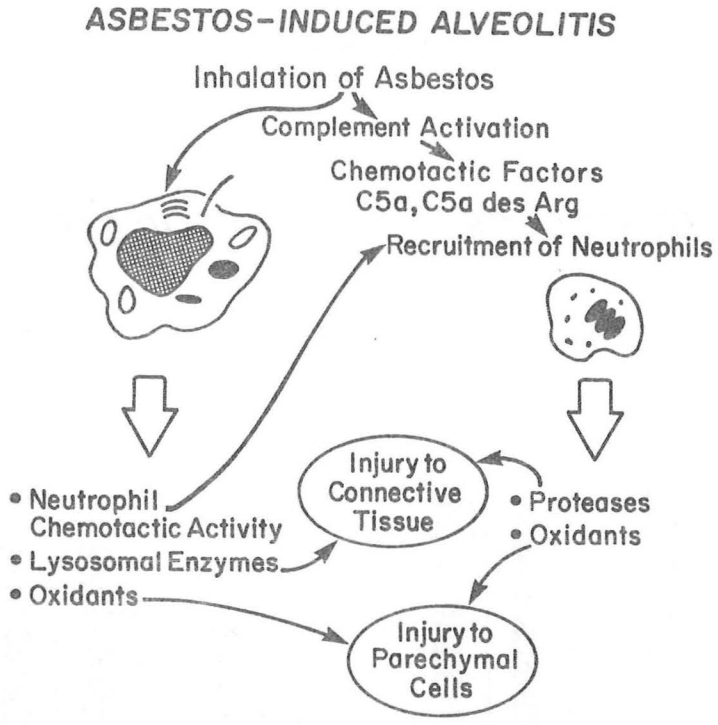
Figure 5



Incubation of asbestos fibers with normal human serum before incubation with macrophages augmented the release of chemotactic factor by the macrophages. In addition, alveolar macrophages from guinea pigs exposed *in vivo* to short chysotile fibers spontaneously release neutrophil chemotactic factor. An additional source of chemotaxins is the complement system. Asbestos activates both the classic and alternative complement pathways and could lead to the direct generation of chemotactic factors within the alveolus (80, 81).

Recruitment of neutrophils to the alveolus has severe consequences for the alveolar structures since the neutrophil is a remarkably potent cell, capable of releasing a broad armamentarium of mediators that can markedly derange the interstitium (Figure 6).

Figure 6



Neutrophil chemotactic factor not only recruits neutrophils to the alveolar spaces but also activates these neutrophils to rapidly release their mediators including connective tissue specific proteases and oxidants (82). Although the functional consequenses of having neutrophils within the alveolar structures in asbestosis has not been critically studied, there is evidence of the consequences of a neutrophil alveolitis in a chronic human disease, idiopathic pulmonary fibrosis. In this disease, there is a clear association between the numbers of neutrophils present and the functional deterioration of these patients (83). It is believed that proteases are likely involved in damaging the alveolar wall matrix components. One neutrophil protease, a collagenase, has been detected in the epithelial lining fluid of patients with IPF and it is assumed that this enzyme is one of the mechanisms by which collagen is deranged. It has also been shown that activated neutrophils are cytotoxic to normal lung parenchymal cells and that these cytotoxic properties are related to the release of reactive oxidant species (84).

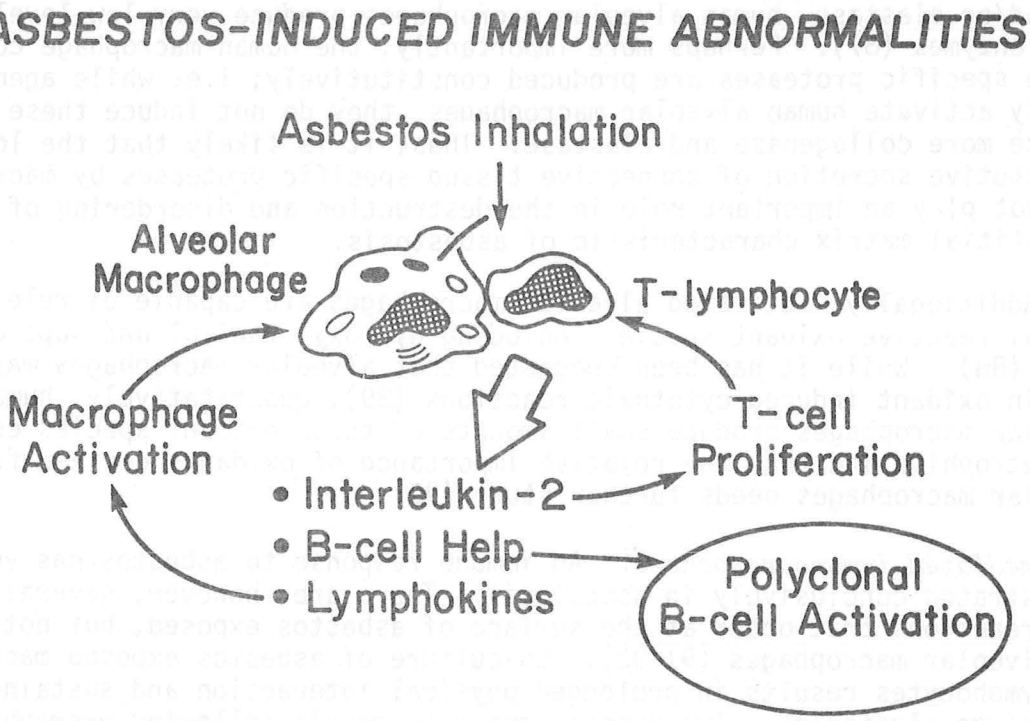
Alveolar macrophages from a variety of experimental animals can be induced to release significant amounts of collagenase and/or elastase (85, 86). Macrophage collagenase can attack collagens I and III and macrophage elastase can degrade elastin. However, there appear to be major differences between human alveolar macrophages and those of experimental animals. While mouse and rabbit alveolar macrophages can be induced to produce large amounts of collagenase and/or elastase, human alveolar macrophages produce very low levels of these enzymes (87). Perhaps more importantly, the human macrophage connective tissue specific proteases are produced constitutively; i.e. while agents clearly activate human alveolar macrophages, they do not induce these cells to produce more collagenase and elastase. Thus, it is likely that the low level constitutive secretion of connective tissue specific proteases by macrophages does not play an important role in the destruction and disordering of the interstitial matrix characteristic of asbestosis.

Additionally, activated alveolar macrophages are capable of releasing several reactive oxidant species including hydroxyl radical and superoxide anion (88). While it has been suggested that alveolar macrophages may play a role in oxidant induced cytotoxic reactions (89), quantitatively, human alveolar macrophages produce small amounts of these oxidant species compared to neutrophils and thus the relative importance of oxidants derived from alveolar macrophages needs further study (90).

Cell mediated immune responses: An immune response to asbestos has yet to be demonstrated conclusively in asbestosis. There are, however, several immune-like reactions that occur at the surface of asbestos exposed, but not control, rat alveolar macrophages (91-93). Co-culture of asbestos exposed macrophages and lymphocytes results in prolonged physical interaction and sustained lymphocyte clustering. Two events appear to result following macrophage-lymphocyte binding. The first event is a blastogenic response noted after 72 hours of incubation which can be abolished by treatment of the dusted macrophages with L-cysteine. The other asbestos related phenomenon, an antigen-like affect, is noted in co-cultures of asbestos exposed macrophages and asbestos exposed lymphocytes. A peak lymphoproliferative response is noted in these cultures after 96 hours of incubation. The latter effect is not abrogated by L-cysteine and requires major histocompatibility complex linked restriction between interacting macrophages and lymphocytes. It thus appears

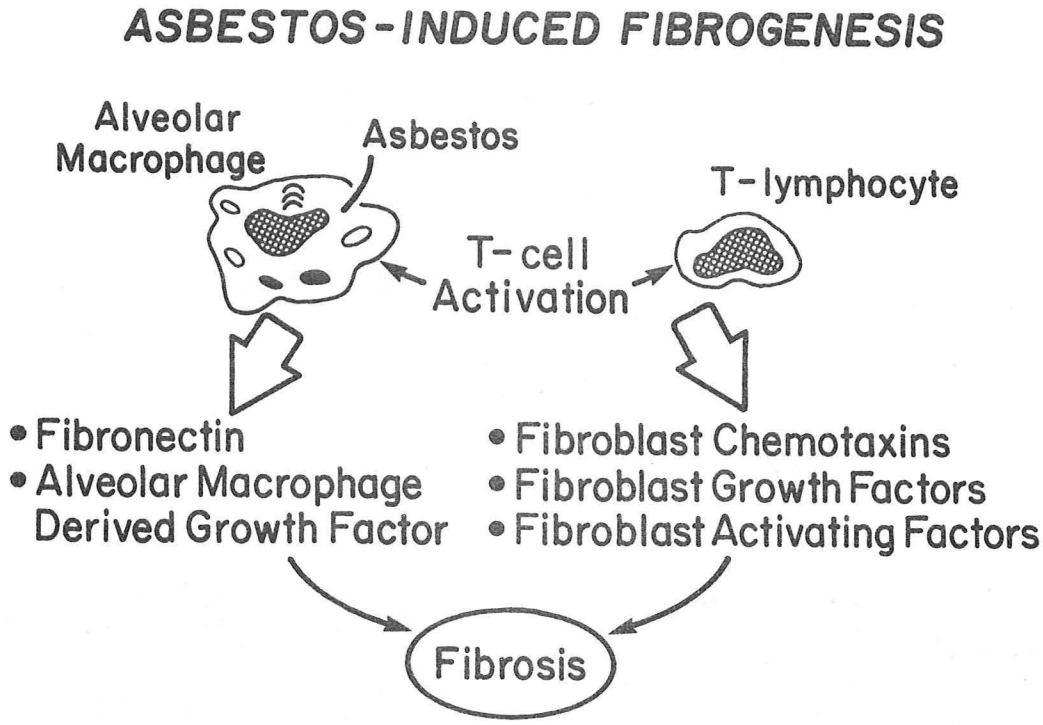
that inhalation exposure to asbestos produces an effect in the alveolar macrophage similar to membrane peroxidation by $NaIO_4$, and that there also may be an asbestos related antigen on or associated with the macrophage surface membrane. If intrapulmonary or systemic cell-mediated immune responses are generated in asbestos exposed individuals, this event could have important implications regarding the pathogenesis of asbestosis (Figure 7). First, activated T cells might provide B cell help and thus explain the polyclonal B-cell activation noted in patients with asbestosis. Secondly, the release of lymphokines has been shown to be involved in macrophage activation (94). The induction of cell-mediated immunity by asbestos exposed macrophages might initiate a complex series of reactions in the lung and systemically, which would be important in the development of pulmonary fibrosis.

Figure 7



Mechanisms of pulmonary fibrosis in asbestosis: Asbestosis is characterized by a progressive thickening of normal alveolar walls by a fibrotic process characterized by an expansion of fibroblast numbers and the collagenous extracellular matrix secreted by these cells (95, 96). Since the fibrotic process is characterized by expanded numbers of fibroblasts (97, 98), mechanisms modulating the development of fibrosis must involve processes that stimulate fibroblast proliferation (Figure 8).

Figure 8

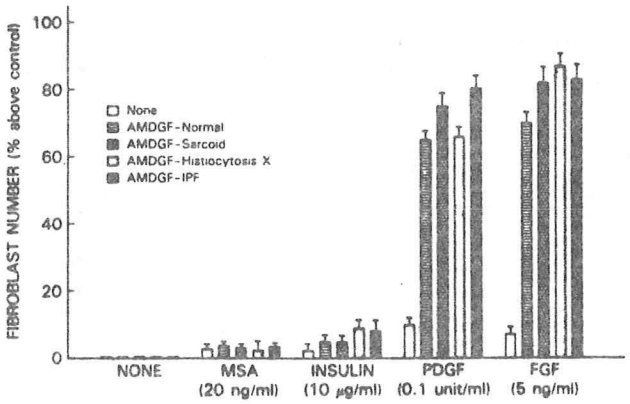


The modulation of fibroblast replication is a complex process believed to be under the dual control of competence factors and progression factors (99). Competence factors such as fibroblast growth factor and platelet derived growth factor act early in G_1, permitting the target cell to respond later in G_1 to progression factors. Progression factors act sometime later in G_1 stimulating the target cell to synthesize DNA and divide. For optimal replication, both a competence and progression factor are required.

Several possible links exist between the chronic alveolitis which characterizes asbestosis and the expansion of fibroblast numbers noted in this disorder. Following exposure to asbestos, alveolar macrophages release a growth factor that can stimulate human lung fibroblasts to replicate (78). This growth factor, termed alveolar macrophage derived growth factor, is an 18,000 Dalton protein that acts as a progression factor to stimulate fibroblast replication in serum free conditions in the presence of competence factors such platelet derived growth factor, fibroblast growth factor or fibronectin (100) (Figure 9).

Figure 9

AMDGF is a Progression Factor

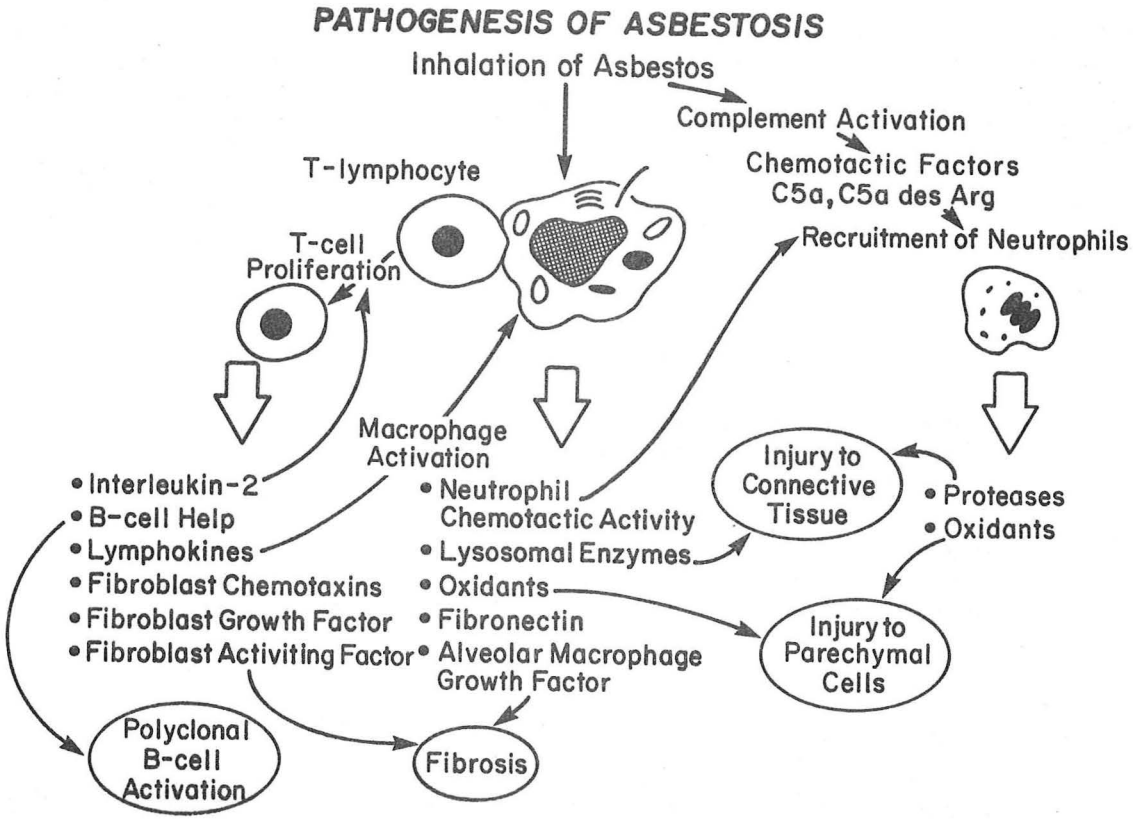


Bitterman, J. Clin. Invest. 72:1807, 1983

The dual control model would suggest that for fibroblast replication to occur optimally within the alveolar structures, in addition to the progression signal provided by AMDGF, the competence signal must also be present. In accord with this prediction, macrophage fibronectin, which is produced in increased amounts in fibrotic lung disorders, is known to act as a competence factor (101). Preliminary studies correlating clinical outcome of patients with interstitial lung disorders with the presence of alveolar macrophages releasing AMDGF and increased amounts of fibronectin suggest that, if both mediators are released, deterioration is very likely, and conversely, if both mediators are not released, deterioration is unlikely (102). In addition, stimulated or activated lymphocytes are known to produce factors which induce fibroblast migration, fibroblast proliferation, and collagen synthesis (103-105). The role of these lymphokines in pulmonary fibrosis remains to be clarified but it is tempting to speculate that activated lymphocytes might also be involved in triggering fibroblast activation and proliferation in the development of fibrosis.

The second mechanism of fibrosis in asbestosis centers around the concept of activated macrophages releasing a factor that stimulates each fibroblast to increase its rate of collagen production independent of effects on cell replication. Heppeleston suggested that macrophages exposed to silica release an activity that causes fibroblasts to increase their rate of collagen production (106). But unfortunately, attempts to repeat these observations have been highly variable and have included decreases in collagen production, no change in collagen production and large increases in collagen production. Reconciling these findings is difficult because of methodologic differences (107-109). However, examined in the context of current concepts of collagen production and growth regulation, it is fair to say that to date, no study clearly demonstrates a major increase in lung fibroblast collagen production induced by a characterized secretory product of alveolar macrophages activated by an environmental agent.

Figure 10



Prognosis and Treatment

The average age of death of patients with asbestos was 49 years before 1940 and 60 years in the early 1960's (110). This longer overall survival has increased the possibility of death resulting from bronchogenic carcinoma and unrelated diseases. Effective treatment of asbestosis requires the prevention of excessive exposure before disease occurs. Medical management of asbestosis is restricted to the symptomatic care given to patients with interstitial fibrosis, whatever the cause. Use of corticosteroids is not advocated, because asbestos remains fixed in lung tissue. Cigarette smoking should be strongly discouraged. Prompt treatment of bacterial pulmonary infection may be particularly important in view of the suggestion that non-specific inflammation may contribute to progression of fibrosis (111). Influenza vaccination is recommended in these patients. For hypoxemic patients attempts should be made to improve oxygenation with home oxygen (112). Any suggestion of neoplasm - hemoptysis, weight loss, or vague chest pain - should be investigated promptly since death in recent series is more often related to cancer than to respiratory failure (110). Finally, the patient should be informed of the causal relationship between asbestos exposure and his disease. There is no real evidence to suggest that the only possible effective therapeutic intervention, namely, to remove the patient from exposure, has any real influence on the outcome of the case. Disease can both appear and progress many years after removal from exposure (113). An area in need of study is the factors which determine this future progression in interstitial fibrosis following asbestos exposure.

Table 10

Treatment of Asbestosis

Steroids not recommended
Discontinue cigarette smoking
Treat pulmonary infections
Influenza vaccine
Oxygen
High suspicion of neoplasms
Inform patient of causal relationship with asbestos

BENIGN ASBESTOS PLEURAL EFFUSION

Exudative pleural reactions which may occur in association with all the asbestos-related lung diseases may also occur as the primary or at least the most prominent clinical manifestation of asbestos exposure. A diffuse exudative pleural reaction following asbestos exposure was first described in 1964 (114). Although this condition was termed "benign", 2 of the 4 patients originally described had developed mesothelioma after 12 years of follow-up. Numerous additional cases have subsequently been reported (115-118). Unlike pleural plaques, asbestos pleurisy involves the visceral as well as the parietal

pleura and is often associated with symptoms and pulmonary functional impairment (118). The clinical features of benign asbestos pleurisy are shown in Table 11. The onset of the effusion is usually subtle. The most frequent presenting complaint is pleuritic chest pain; however, when the onset is acute, there may be associated fever, leukocytosis and elevation of the sedimentation rate.

Table 11

Clinical Features of Benign Asbestos Pleural Effusion

Subacute or chronic course with pleurisy

Effusions are usually unilateral but may be bilateral and recurrent

Subjects more likely to develop asbestosis and mesothelioma

Wright, Thorax 35:31, 1980
Gaenster, Ann. Intern. Med. 74:178, 1971
Eisenstadt, JAMA 192:419, 1965

Physical examination usually reveals only signs of effusion, with dullness to percussion and decreased breath sounds. In cases with associated asbestosis, basilar crepitant rales may be audible. Standard chest radiography may show, in addition to the fluid, some combination of asbestosis, hyaline or calcified pleural plaques or exudative pleural thickening.

The pleural effusion may be unilateral or bilateral or may be recurrent. Regression of an effusion on one side may be followed by accumulation on the other. Up to four separate occurrences have been documented in one patient. Patients who develop benign asbestos pleurisy have been shown to be more likely to develop asbestosis or mesothelioma (118).

The pleural fluid characteristics in benign asbestos pleural effusion are shown in Table 12. The fluid is often hemorrhagic, but can be serous or fibrinous. The fluid is exudative with protein contents ranging between 3.7 and 7.5 grams per deciliter. Eosinophils may predominate in some patients and lymphocytes in others. Cultures and cytologic examination of aspirated fluid are negative and the pleural fluid shows no diagnostic features. Few asbestos fibers can be found in pleural biopsies but these fibers are numerous in the subpleural lung which usually shows some degree of alveolitis.

Table 12

Pleural Fluid Characteristics
In Benign Asbestos Pleural Effusion

Serosanguinous fluid

Exudative pleural fluid

Pleural fluid shows no diagnostic features

Few asbestos fibers in pleural biopsies
but many asbestos fibers in subpleural lung

Wright, Thorax 35:31, 1980
Gaenster, Ann. Intern. Med. 74:178, 1971
Eisenstadt, JAMA 192:419, 1965

The diagnosis of benign asbestos pleural effusion is fraught with hazard. The criteria for diagnosis of benign asbestos effusion are a prior history of asbestos exposure, absence of any other predisposing cause for effusion and spontaneous remission. It cannot be made without long term follow-up to assure that complete resolution has occurred. Even in such cases, an occult cause such as thromboembolic disease may be responsible. Thus, the diagnosis of a benign asbestos pleural effusion should be considered a diagnosis only by exclusion. It should be remembered that pleural effusions related to asbestos exposure may be secondary to asbestosis, bronchogenic carcinoma, cor pulmonale or malignant pleural mesothelioma.

Table 13

Diagnostic Criteria for Benign Asbestos Pleural Effusion

Prior history of asbestos exposure
Absence of other predisposing causes of effusion
Spontaneous remission
Differential diagnosis:

- Asbestosis
- Bronchogenic carcinoma
- Mesothelioma
- Cor pulmonale

PLEURAL PLAQUES

Clinical Presentation

The parietal pleural plaque is the most common asbestos related disorder, occurring in more than 50 percent of those patients with long term asbestos

exposure (119-121). Prevalence appears to increase in relation to total asbestos dosage and generally plaques do not appear until 20 or more years after the first exposure to asbestos (122). All forms of asbestos appear to be capable of producing plaques although anthophyllite may be associated with the highest rate (5). The most usual clinical presentation is as an incidental radiologic finding in an asymptomatic patient. Pleural plaques in the absence of pulmonary fibrosis are rarely associated with respiratory symptoms including dyspnea (16). Occasionally patients with extensive pleural involvement will complain of breathlessness and rarely will have chest pain (3, 5). Studies of pulmonary function in patients with pleural plaques but without parenchymal fibrosis have demonstrated no impairment, although small but significant reductions of lung volume have been reported (123). Pleural plaques themselves are neither harmful nor precancerous; however, they indicate that enough time has elapsed since initial exposure to increase the risk of asbestosis and cancer. The decreasing intensity of exposure in recent years may eventually result in a greater prevalence of pleural disease because fewer asbestos workers will have died early from pulmonary fibrosis (3). There is some evidence that persons exposed to asbestos who have pleural plaques are at greater risk of developing neoplasia than those without plaques (124). Series of patients with bronchogenic, laryngeal and gastrointestinal cancer have a higher prevalence of plaques than the general population (122). Plaques are not thought to be a direct precursor of malignant mesothelioma.

Table 14

Clinical Characteristics of Pleural Plaques

Most common asbestos related disorder
Occur after over 20 years of asbestos exposure
Present as an incidental radiologic finding
Normal pulmonary functions
Greater risk of developing neoplasia

Becklake, Am. Rev. Respir. Dis. 114:187, 1976
Casey, Clin. Chest Med. 2:179, 1981

Radiographic Findings

Radiographically, pleural plaques appear as diffuse or circumscribed pleural thickening commonly located on the aponeurotic portion of the diaphragm and on the posterior lateral or lateral chest wall between the sixth and tenth ribs (39). They may have smooth, nodular or irregular contours. Plaques are most often bilateral but often are not symmetric. Pleural plaques are most clearly defined when viewed tangentially, that is in profile along their long axes. A routine PA chest radiograph will distinctly demarcate a plaque located on the inner surface of the lateral chest wall, because the X-ray beam then parallels the tangential plane of the plaque. The reverse is true for a plaque involving the anterior or posterior chest wall. Here the tangential

plane of the plaque is perpendicular to the X-ray beam and PA films will show the plaque in a frontal orientation. When viewed frontally, small non-calcified plaques are perceived as ill-defined, irregular densities adjacent to the ribs.

Only a small portion (about 15 percent) of pleural plaques identifiable in necropsy are detectable by standard PA radiography (125). Since the posterolateral chest wall is the most commonly involved site, plaques will be demonstrated best by films taken in the oblique position. For these reasons, it is recommended that both right and left oblique views be obtained routinely in radiographic examinations of the chests of persons suspected of having asbestos related disease. Calcified pleural plaques are more readily discerned radiographically than non-calcified plaques. If the X-ray beam strikes the margin of a calcified plaque tangentially, calcification appears as a dense white line paralleling the chest wall, diaphragm or cardiac border. When the X-ray beam strikes the surface of a calcified plaque frontally, it tends to present an irregular and unevenly dense pattern that has been compared to the border of a holly leaf or a map (3, 39). Routine chest X-rays show evidence of interstitial pulmonary disease (asbestosis) in about one-third of patients with calcified pleural plaques. Conversely, more than half of those patients with extensive pulmonary fibrosis eventually develop pleural calcifications that are visible on routine chest radiography (39, 40). Computer tomography is more sensitive than conventional chest radiography in detecting pleural plaques. Once present, the plaques tend to progress and to calcify. The incidence of calcification increases in proportion to the time since initial exposure. The incidence of pleural calcification is 10 percent 20 to 29 years after first exposure, but is 60 percent 40 or more years afterwards (126).

Pathology

Grossly, parietal plaques are irregularly shaped, shiny, gray-white, well demarcated elevations up to 1 cm in thickness. The great majority of plaques are located on the parietal pleura although visceral pleural plaques have been described in interlobar fissures (121, 127). Plaques are rarely encountered in the apices, costophrenic angles or near the costal cartilages. Microscopically, plaques are composed of dense bands of avascular collagen with hyaline changes in a tight basket weave pattern. They are relatively acellular with only a few fibroblasts present. Elastic stains demonstrate continuous parietal pleural connective tissue beneath the plaque suggesting that plaques arise extrapleurally between the pleura and its covering mesothelial layer. Asbestos bodies are not seen in pleural plaques but uncoated fibers visible by electron microscopy may be present. Calcification is of a dystrophic type occurring in acellular, degenerating collagen.

The pathogenesis of pleural plaques remains unclear. One hypothesis is that pleural plaques result from trauma to the parietal pleura during breathing by sharp asbestos spicules penetrating the pleura. This trauma is believed to produce hemorrhage and subsequent organization of the blood clot in a manner comparable to the process seen in large hemothoraces (128). Against this theory is the failure to demonstrate inflammatory exudates and the conspicuous absence of adhesions in association with pleural plaques. Also intracellular transportation via pulmonary lymphatics and then retrograde spread via the

chest wall lymphatics due to the massaging action of the respiratory muscles does not seem likely in the absence of hilar or mediastinal lymph node enlargement, neither of which has been found in association with pleural plaques. Hillerdal has recently suggested that asbestos fibers, particularly long ones, tend to move towards the lung periphery and to eventually enter the pleural space. Once in the pleural space, these fibers are ingested by macrophages which in turn stimulate sub-mesothelial fibroblasts (129). While this latter theory is plausible, it is most realistic to accept the conclusion that the pathogenesis of pleural plaques that occur in association with asbestos exposure is unknown.

Hyalinosis Complicata

One less frequent variant of benign pleural thickening deserves separate mention because of the clinical confusion it causes. This condition has been termed hyalinosis complicata as opposed to hyalinosis simplex for individuals with pleural plaques as described in the preceding section. Hyalinosis complicata is rarely seen in individuals with calcified pleural plaques. Hyalinosis complicata or exudative pleural rind is characterized clinically by chest pain and dyspnea, with subsequent development of restrictive lung disease as the rule rather than the exception. Death is often due to the pleural lesions, or rarely mesothelioma (130). Histopathologically, this is an acute exudative inflammatory process with a coexistent exudative effusion. An extensive pleuritic reaction results, which involves both the visceral and parietal pleura and obliterates the pleural space. It is not clear whether this reaction is specific for asbestos or whether it can occur in individuals without exposure to asbestos. The differentiation between hyalinosis complicata and mesothelioma is a most difficult one, and individuals with this diagnosis should be followed closely for their lifetime before concluding that mesothelioma is not present.

BRONCHOGENIC CARCINOMA

Epidemiology

A substantial proportion of workers exposed to asbestos dust can be expected to die of lung cancer. Lynch and Smith described a case of lung cancer in man with pulmonary asbestosis in 1935 and Doll performed the first retrospective cohort study in 1955 finding 11 lung cancer deaths in a population of British asbestos textile workers in which 0.8 deaths would have been expected from national mortality statistics (131, 132). Subsequently a large number of cohort studies have confirmed the association between asbestos exposure and lung cancer death (133-135), and this association is now accepted as being causal in nature. The frequency with which lung cancer occurs in patients with pulmonary asbestosis has been reported to be as high as 55 percent in one series (136). It has recently been estimated that 20 to 25 percent of workers heavily exposed to asbestos will develop bronchogenic carcinoma (137). The emergence of lung cancer as an important threat to the health of asbestos workers is attributed to the improvement in dust conditions. With less mortality from asbestosis, workers now survive through the long latent period of lung cancer. Typically, the latency period is greater than 20 years and in general, the greater the exposure to asbestos, the higher the risk of developing lung cancer and the shorter the latency period (138).

The relationship between exposure to asbestos and cigarette smoking in the etiology of bronchogenic carcinoma has only recently been clarified. Because of the high prevalence of smoking among asbestos workers it has been difficult to define the risk in non-smoking workers. Recent data from the large cohort study of Selikof, et al., are shown in Table 15 (24). The lung cancer death rate, standardized for age and expressed per 100,000 man-years of observation, was 11.3 for men who did not smoke or work with asbestos. The rate was 122.6 for smokers not exposed to asbestos. The rate was 58.4 in non-smoking asbestos workers, a five-fold increase over the control population. The rate for smoking asbetos workers was 601.6. Thus the relative risk of asbestos exposure is similar in smoking and non-smoking groups. These data demonstrate that asbestos exposure increases the risk of dying from lung cancer in non-smokers; however, since the incidence is low in non-smokers, this increased risk does not produce a large number of cancers. Smoking and asbestos interact in a multiplicative manner. When the high incidence of lung cancer in smokers is multiplied by the relative risk associated with asbestos exposure an extremely high risk ensues (24, 138).

Table 15

Relationship Between Asbestos Exposure, Smoking and Bronchogenic Carcinoma

Bronchogenic Carcinoma	Incidence per 100,000 man-years	Relative risk ratio
Non-smoking men	11.3	1
Smokers, no asbestos	122.6	10
Non-smoker, asbestos worker	58.4	5
Smoker, asbestos worker	601.6	60

Selikoff, JAMA 242:458, 1979

Clinical Presentation

The clinical presentation, radiology and prognosis of asbestos workers with lung cancer are no different from other patients with this tumor. It has been suggested that there is a high prevalence of adenocarcinoma in asbestos workers when compared to other series of lung cancer patients. The incidence of adenocarcinoma in several series of patients with asbestos exposure and lung cancer is shown in Table 16 (139-143). These data should be interpreted with caution. The nature of biopsy material and the availability of special techniques to classify poorly differentiated lung tumors can affect the proportion of a specific cell type. Furthermore, it appears that adenocarcinoma is becoming the most common cell type of non-asbestos exposed patients as well (144). Therefore, although evidence suggests that adenocarcinoma is more common in asbestos patients, a specific cell type of cancer in an asbestos worker has little medical or legal significance (136). Crocidolite, despite a high hazard for mesothelioma, seems to carry a lower risk for lung cancer than other fiber types (25).

Table 16

Incidence of Adenocarcinoma in
Asbestos Exposed Patients with Bronchogenic Carcinoma

Author	Number of Patients	Percent Adenocarcinoma
Heuper	104	19
Hourihan	17	35
Kannerstein	50	22
Warnock	30	43
Whitwell	88	34

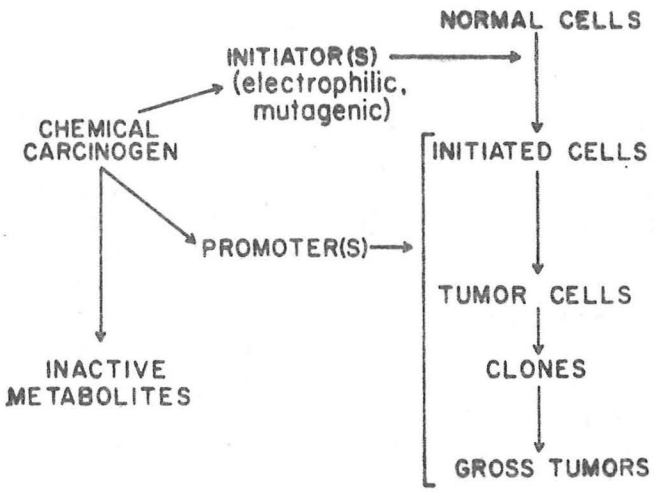
In the great majority of cases, asbestos associated lung cancer arises in areas of parenchymal fibrosis (136), although this is not invariably the case. These tumors tend to occur peripherally more often and more frequently in the lower lobes in populations exposed to asbestos. Because asbestos workers have an extremely high risk for the development of bronchogenic carcinoma, a periodic examination with chest X-ray and sputum cytology has been advocated to attempt early identification and perhaps curative treatment of malignancy. The effectiveness of this approach remains to be demonstrated and there is at the present time no basis for recommending mass screening programs of this sort (145). Since a chest radiograph is already part of the yearly medical examination mandated by OSHA statutes, it seems reasonable to obtain a chest X-ray for individual asbestos workers who request either general medical examinations or specific examinations for cancer or asbestos related disease. This would apply particularly to those over 45 years old who have been excessive smokers of cigarettes and who were first exposed to asbestos at least 20 years previously.

Mechanisms of Asbestos Carcinogenesis

Carcinogenesis is thought to be a multi-step process that can be subdivided into sequential stages of initiation and promotion (146) (Figure 11). Initiation is an irreversible process produced by the application of a chemical carcinogen such as a polycyclic hydrocarbon (PCH) (147). Numerous polycyclic hydrocarbons are found in cigarette smoke. The initiator either acts directly with the DNA of the cell or requires metabolic activation by cellular enzymes. This interaction can result in malignant change. On the other hand, the process of promotion is reversible and is caused by prolonged exposure to a substance that generally is not carcinogenic when administered alone. Tumor promotion has been shown to be important in the pathogenesis of experimental neoplasms of the lung (148).

Figure 11

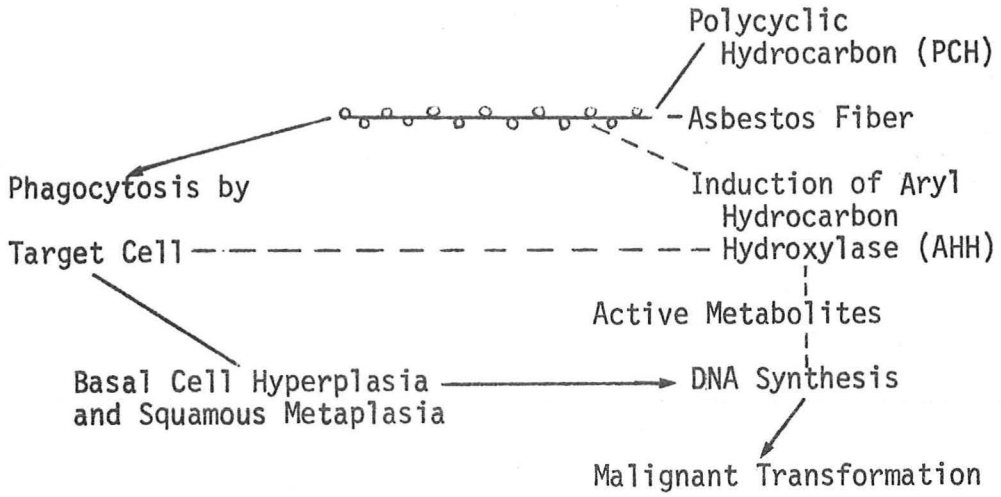
Induction of Cancer by a Chemical Carcinogen



Promotors have several characteristics: a) attach to and possibly enter into target cells; b) stimulate cellular division while inhibiting differentiation; and c) induce the activity of plasma membrane enzymes such as Na^+-K^+dependent ATPase (148, 149). As shown in Figure 12 asbestos has many of the properties of a classic tumor promotor. Asbestos enters not only alveolar macrophages but has been found in pre-malignant tracheal epithelial cells after exposure to these fibers. Proliferation and squamous metaplasia are induced in the respiratory tract mucosa of rodents *in vitro* as well. In addition, increased activity of the plasma membrane enzyme, Na^+-K^+ dependent ATPase has been documented (150, 151).

Figure 12

Asbestos-Induced Carcinogenesis



Mossman, Environ. Res. 25:269, 1981

An alternate related mechanism is worthy of consideration. Asbestos can be phagocytized by the bronchial epithelium and can be transported intracellularly both free in the cytoplasm and in phagolysosomes (152). These fibers might serve as a physical carrier of carcinogens in cigarette smoke to the basal cell, the presumptive progenitors of neoplasm. Transfer of polycyclic aromatic hydrocarbons to and through biological membranes occurs promptly and efficiently when the hydrocarbon is adsorbed to asbestos as shown in Figure 12. Covalent binding of PCH to the DNA of a target cell is essential in the initiation of carcinogenesis (147). For this to occur, PCH must be metabolized to a reactive product by the aryl hydrocarbon hydroxylase (AHH) system (147). It is likely that in addition to transferring PCH to the effector cell, asbestos may play a role in the metabolism of PCH by respiratory epithelial cells to reactive carcinogens. Asbestos potentiates the AHH-inducing effects of a known enzyme inducer, 3MC. Significant increases in the AHH activity were observed when crocidolite fibers and 3MC were added simultaneously to the cultures. Thus, the hypothetical scheme of asbestos carcinogenesis includes asbestos related transportation of PCH into basal cells, induction of AHH metabolism of PCH, and stimulation of these cells metabolically in a fashion which causes their de-differentiation.

Treatment

Asbestos workers should be advised to stop smoking. There is evidence suggesting that cessation of cigarette smoking decreases the high risk of cancer observed when these two carcinogenic influences are combined (24). The recommended treatment for non-small cell bronchogenic carcinoma regardless of the patient's occupation is surgical extirpation as reviewed in a previous Grand Rounds by Dr. Robertson. For asbestos workers with bronchogenic cancer, there are several special concerns. First, there is the possibility of associated

pulmonary fibrosis (asbestosis) severe enough to prohibit surgery. Secondly, there is a tendency for tumors to be peripheral and multiple. Preservation of as much functioning lung tissue as possible is a major surgical consideration. These concerns dictate careful assessment of pulmonary function preoperatively. Therapy for asbestos related small cell bronchogenic carcinoma is the same as for other small cell cancers.

DIFFUSE MALIGNANT MESOTHELIOMA

Epidemiology

While mesothelioma is a rare tumor, having an incidence of one per one million per annum in the general population, the association of mesothelioma with asbestos exposure has been consistent in all parts of the world using both case control and cohort methodologies (3). The most disconcerting aspect of the relationship between malignant mesothelioma and asbestos exposure is its documented association with apparently low levels of exposure for relatively brief periods in the remote past.

The great majority of patients with diffuse malignant mesothelioma will recall exposure to asbestos (3). Often the relevant exposure was in the distant past and does not reflect the patient's current occupation. The exposure may have been quite brief although studies have demonstrated an increased risk for malignant mesothelioma with greater intensity or duration of exposure (152). The period of latency before development of diffuse malignant mesothelioma is usually more than 30 years, often more than 40 years (3, 5, 16). Most patients have had occupational exposure and this is reflected in the predominantly male sex ratio and mean age greater than 40 years in most reports (153). Diffuse malignant mesothelioma has, however, been reported in persons whose only exposure was the result of residence in the vicinity of an asbestos factory (154) or in the household of an asbestos worker (15).

The relative risk of developing diffuse malignant mesothelioma varies with occupation, probably as a result of differing intensities of exposure and also because of the specific types of asbestos fibers being used. Crocidolite seems to be the most potent type followed by amosite and chrysotile. Anthophyllite very rarely produces diffuse malignant mesothelioma if at all. Despite the frequent occurrence of benign pleural lesions in Finland, where only anthophyllite was mined, diffuse malignant mesothelioma remains very rare. This observation is evidence against the notion that pleural plaques are a direct precursor of diffuse malignant mesothelioma.

There does not appear to be any interaction between cigarette smoking and asbestos exposure in producing diffuse malignant mesothelioma. While pleural and peritoneal mesothelioma are clearly associated with asbestos exposure, mesotheliomas arising in other sites such as the pericardium and tunica vaginalis are extremely rare and have not been linked to asbestos (5).

Clinical Presentation

The incidence of pleural mesothelioma in males predominates over females by approximately four to one (152-155) (Table 17). Because of the long

period needed following asbestos exposure, most patients are older than 50 years at death with a mean age of 55 to 65 in most series. The onset of symptoms is usually insidious, and symptoms may be entirely absent or minimal when the disease is discovered. Disease progression elicits the common symptoms of chest pain, dyspnea, cough and gradually increasing weight loss accompanied by pronounced asthenia. Chest pain is the most common complaint and eventually becomes the incapacitating symptom in most patients. Because it is caused by infiltration of the chest wall, the pain is usually localized over the involved side but may radiate to the shoulder and arm. The pain commonly has a dull gnawing quality but may vary from mild discomfort to a severe neuralgic pain and rarely has a pleuritic quality. Dyspnea is proportional to the disease stage, occurring with physical exertion in the beginning but later becoming a constant symptom. Cough is a less common symptom and is not usually present until the disease encroaches on the mediastinum.

The later stages of disease are marked by aggravation of all symptoms and rapid weight loss. Some patients have irregular episodes of low grade fever. In the terminal stages there is marked dyspnea, orthopnea, diaphoresis, cachexia and severe chest pain that is only partially releaved by large doses of narcotics. Rarer symptoms include arthralgic pain with hypertrophic pulmonary osteoarthropathy (156) syncopal attacks from hypoglycemia (157) and generalized anasarca from pericardial involvement or obstruction of the inferior and superior venae cavae (158).

Table 17

Clinical Presentation of Malignant Mesothelioma

Clinical Feature	Percent of Patients
Sex	
Males	74
Females	26
Symptoms	
Onset	
Acute	4
Insidious	96
Chest pain	69
Dyspnea	68
Cough	32
Fatigue, weight loss	20
Fever	13
Asymptomatic	5
Physical Exam	
Pleural effusion	78
Clubbing	8
Swollen joints	1

Antman, Semin. Oncol. 8:313, 1981
Chahinian, Ann. Intern. Med. 97:746, 1982
Legha, Ann. Intern. Med. 87:613, 1977

Physical findings vary with the disease stage. Most patients initially present with signs of fluid in the involved hemithorax (Table 17). Dullness and decreased breath sounds at the base of the involved hemithorax are usually the only abnormal physical findings. These findings may be subtle and are often missed prior to the first chest roentgenogram. The right side is initially involved in two-thirds of patients. Clubbing of the fingers and toes is found in approximately 10 percent of patients. Because patients may not initially appear chronically ill, they are often sent home with reassurance.

In the more advanced disease, local chest involvement is more marked and there may be obvious enlargement of the affected hemithorax, bulging of intercostal spaces, and displacement of the trachea and mediastinum to the unaffected side (158). Local tumor growth may also depress the diaphragm and displace the liver and spleen, giving the impression of hepatomegaly or splenomegaly. A pericardial or pleuro-pericardial rub is not uncommonly heard after removal of all pleural fluid. Supraclavicular and axillary lymph node enlargement, subcutaneous nodules in the chest wall, and rib tenderness may be found in cases of advanced disease (159). In cases with advanced disease contraction of the affected hemithorax may occur leading to restriction of chest wall movement and eventually a frozen chest, with flattening of the infraclavicular region and immobility of the chest wall (160).

The tumor has a propensity for growth along the needle tracts after thoracentesis or along the scar of a thoracotomy incision (159, 160). Encroachment on the mediastinal structures may lead to neuropathic signs such as vocal cord paralysis or Horner's Syndrome (161). Chest wall invasion affecting intercostal nerves often leads to anesthesia or altered sensation in the skin of the chest wall and abdomen. Congestion and edema may develop in the upper trunk or lower limbs because of compression of the superior or inferior venae cava, or both.

Radiographic Findings

A unilateral pleural effusion is the most common abnormality (162, 163). On removal of the fluid, the pleura may show gross thickening or nodularity, which is commonly first noted at the bases. Induced pneumothorax after thoracentesis may aid in showing early thickened pleura or small nodular densities. Late in the disease, tomograms or an over-penetrated film will show compressed lung surrounded on all surfaces by a layer of tumor two to three centimeters thick. In addition to the mesothelioma induced changes, signs of asbestosis such as interstitial pulmonary fibrosis, pleural plaques and calcification are of positive differential diagnosic value. In the later stages, the mediastinum may be widened by involvement of the lymph nodes. The pericardium may be infiltrated with the tumor and the resulting effusion may enlarge the cardiac silhouette. Extrapleural extension showing as soft tissue masses or radiologic evidence of rib destruction may occur and is highly suggestive of malignant mesothelioma (163). Hydropneumothorax occurs rarely.

Diagnosis

Pleural fluid findings in pleural mesothelioma are shown in Table 18. The pleural fluid is usually straw colored but has been reported to be serosanguinous in about 30 to 50 percent of cases (152-155). The effusions

generally have a tendency for rapid reaccumulation requiring frequent aspirations and the fluid becomes increasingly hemorrhagic with repeated taps. The fluid is usually an exudate, with high protein concentrations ranging from 3.5 to 5.5 grams per 100 cc (161). Elevated levels of lactic dehydrogenase are usually present. Detection of an elevated concentration of hyaluronic acid has been considered helpful in the diagnosis of diffuse mesothelioma. However, elevated hyaluronic acid is far from being a specific test and is only moderately sensitive for the differential diagnosis of mesothelioma (164-167). When the concentration of hyaluronic acid is very high (greater than .8 milligrams per ml) this finding should lead one to consider the possibility of an underlying mesothelioma (167).

Table 18

Pleural Fluid Characteristics of Pleural Mesothelioma

Straw colored or serosanguinous fluid
Fluid reaccumulates rapidly
Exudative pleural fluid
Marked elevation of hyaluronic acid suggests the diagnosis
Malignant cells present in 20 percent of cases

Antman, Semin. Oncol. 8:313, 1981
Chahinian, Ann. Intern. Med. 97:746, 1982
Legha, Ann. Intern. Med. 87:613, 1977

There is considerable difference of opinion regarding the diagnostic value of exfoliative cytology in malignant mesothelioma (168-170). The pleural fluid generally is very cellular, containing a mixture of normal mesothelial cells, differentiated and undifferentiated malignant mesothelial cells and varying numbers of lymphocytes, histiocytes and polymorphonuclear leukocytes. In these collected observations, 20 percent of the cases showed no clue of the malignant nature of the effusion. Undifferentiated malignant cells without mesothelial cell characteristics were found in another 20 percent of cases. Approximately 50 to 60 percent of the cases had typical mesothelial cells. The diagnostic value of cytology is limited because of the subtle differences between benign and malignant mesothelial cells. Mesothelial hyperplasia and hypertrophy is not uncommon in benign pleural effusions, and the cells can be easily mistaken for malignant cells and vice versa.

The accuracy of the diagnostic procedures in a large series of pleural mesothelioma is listed in Table 19 (171). Unfortunately the standard approach of aspiration, fluid analysis and cytologic studies tends to be unrewarding. Needle biopsy of the pleura is only somewhat more helpful. An open thoracotomy is generally required to furnish sufficient material for correct diagnosis. Multiple biopsies from different pleural areas should be taken because of the variable histology seen in this tumor. The gross pathology and thoracotomy is usually characteristic and suggests the diagnosis to the experienced surgeon.

The final diagnosis rests on detail histologic examination aided by histochemical studies. Electron microscopy may be of value in certain cases (172-173).

Table 19

Efficacy of Diagnostic Procedures for Mesothelioma

Method	Number Examined	Correct Diagnosis
Cytology of fluid	172	4%
Needle biopsy	69	26%
Thoracotomy	175	70%

Elmes, Q. J. Med. 45:427, 1976

The following criteria establish the diagnosis of mesothelioma: 1) no primary tumor capable of serosal spread is present; 2) tumor tends toward superficial growth along serosal planes with only shallow invasion; 3) metastases occur only to regional lymph nodes; and 4) the histologic picture is one of epithelial-type cells, or mesenchymal-type cells or mixed. Using these criteria, it is apparent that a definitive diagnosis of mesothelioma rests heavily on post-mortem findings to establish with certainty the absence of another primary tumor and the extent of direct invasion and metastatic spread. Any diagnosis made during life should be considered "probable" mesothelioma (16, 174, 175).

Pathogenesis of Mesothelioma

The pathogenesis of mesothelioma is poorly understood. Experimental studies by Stanton (176, 177) provide an intriguing basis for speculation about the pathogenesis of this tumor. The dimensions of the fiber, but not the chemical composition, were found to be the critical determinants affecting the development of tumors in rats. Long, thin fibers of a variety of types proved carcinogenic when introduced into the pleural space, whereas short fibers and those with a relatively broad diameter failed to induce mesotheliomas. These findings are consistent with epidemiologic observations documenting the relative common occurrence of tumors in populations exposed to grades of crocidolite consisting predominantly of long, thin fibers and the rarity of tumors in persons exposed to comparatively blunt, shorter fibers of amosite and anthophyllite (178-180). A fibrous mineral, erionite, has recently been associated with the occurrence of pleural fibrosis and mesothelioma in a rural area of Turkey where commercial mining of asbestos does not occur (181). Since the fibers of this mineral do not possess the chemical properties of asbestos but are morphologically similar to crocidolite fibers, the observation is consistent with the experimental findings of Stanton and his associates. Experimental studies have documented 14 different fibrous materials which produce malignant "fibrous neoplasms" following implantation in the pleural or peritoneal cavities of animals (182).

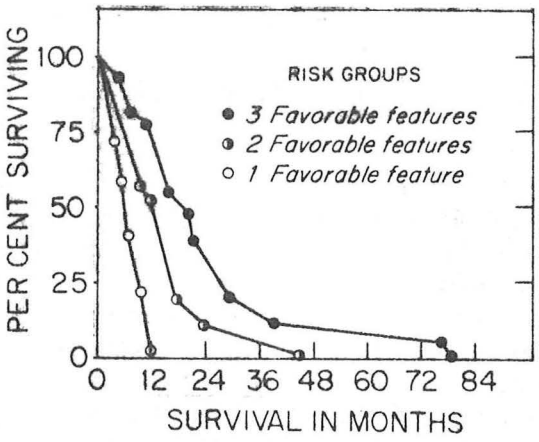
The mechanism of malignant transformation of mesothelial tissues is obscure. Surprisingly little experimental information has accumulated, although there is reason to believe that the lesions may be comparable to the foreign body sarcomas induced subcutaneously in animals by sheets of plastic, glass and metal. The cell of origin is not certain, and some tumors are made up of malignant serosal cells, whereas others have the histologic features of fibrosarcoma. Mesothelial cells phagocytize asbestos and proliferate when exposed to asbestos *in vitro* (183, 184) but malignant transformation has not been demonstrated after exposure of cultured mesothelial cells to asbestos. Co-carcinogenic substances and cigarette smoke do not appear to be pathogenic factors *in vivo*.

Therapy

Certain factors dictate a favorable prognosis for mesothelioma patients, including epithelial cell type, age below 65 and pleural involvement (Figure 13) (55). When all three favorable features were present, median survival from diagnosis was 19 months and 2 year survival was 33 percent in 33 patients. In contrast median survival from diagnosis was 11.5 months for 28 patients with any 2 favorable features and 6 months for 8 patients with any single favorable feature.

Figure 13

Prognostic Factors in Mesothelioma

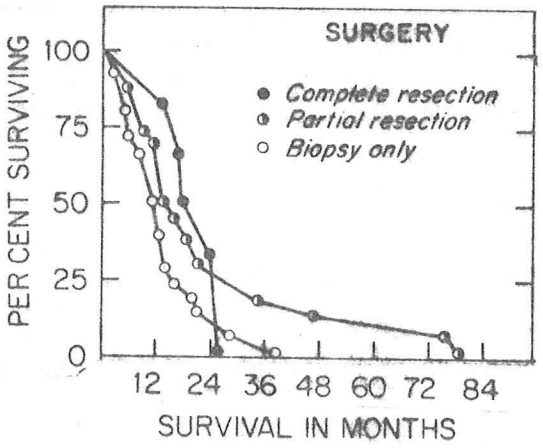


Chahinian, Ann. Intern. Med. 96:746, 1982

Regardless of its extent, radical surgery was never curative, but median survival from diagnosis in this group reached 18 months with a survival rate of 84 percent at 1 year and 33 percent in 2 years (Figure 14). Partial decortication and pleurectomy leads to good palliation of chest pain and prevention of recurrent pleural effusion in some patients. Palliative surgery was useful to improve quality of life and had a moderate beneficial effect on survival. Survival rates were 57 percent at 1 year and 27 percent at 2 years versus 43 percent and 14 percent respectively for patients who have biopsy only. Conventional radiotherapy has been ineffective (185).

Figure 14

Surgical Response in Mesothelioma

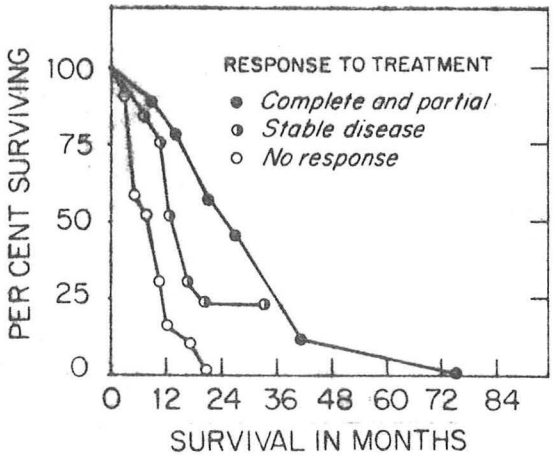


Chahinian, Ann. Intern. Med. 96:746, 1982

Among the various chemotherapeutic agents, doxorubicin has been the most widely tested and appears to be the most active at this time (155). Doxorubicin alone induced remission in only 7 of 51 patients including 2 complete responses (155). Median survival from first chemotherapy was 7.5 months. Doxorubicin and 5-azacytidine combinations have also been studied with overall median survival from first chemotherapy being approximately 13 months (155). In rare instances, long term response from systemic chemotherapy occurs. Four of 57 patients from a recent series were complete responders and lived between 27 and 76 months from the onset of chemotherapy (Figure 15).

Figure 15

Response to Chemotherapy in Mesothelioma



Chahinian, Ann. Intern. Med. 96:746, 1982

AN APPROACH TO THE INDIVIDUAL PATIENT SUSPECTED OF HAVING AN OCCUPATIONAL PULMONARY DISEASE

The practicing physician is frequently asked to evaluate a patient in order to determine whether the patient's pulmonary complaints are related to a specific occupational exposure. Individuals exposed to asbestos may present to their physician with knowledge of their exposure and fears of its consequences, but more commonly, a patient with definite evidence of disease is unaware of his exposure history or does not consider it relevant to his present complaint. The physician who encounters individuals presenting with a history of exposure must document and quantitate the exposure history, identify the type of asbestos, take appropriate diagnostic steps to establish the presence or absence of asbestos related disease, reassure the worried well and institute an appropriate program for those patients with disease. In dealing with symptomatic patients, the physician must have a high degree of suspicion of the observed disease being related to asbestos exposure if the correct diagnosis is to be reached. Once the association between asbestos exposure and disease is suspected, the physician is able to seek a history of exposure, look for other consequences of asbestos exposure, confirm the diagnosis and provide appropriate treatment.

The general approach to a patient who is suspected of having occupational pulmonary disease is shown in Table 20. The approach has three components, each providing valuable information. Whereas a single component, in itself, may not be sufficient for making a diagnosis, several components together usually lead to the correct diagnosis.

Table 20

General Approach to a Patient Suspected of Having Occupational Pulmonary Disease

A. Medical history
Detailed occupational history

Identification of material
Amount of exposure

Physical exam
Chest Xray
Pulmonary function tests

Spirometry
Diffusing capacity

B. Special studies (more detailed lung function, immunologic and skin tests; sputum, blood, urine and tissue analyses; special X-ray studies; fiber-optic bronchoscopy; bronchoalveolar lavage; etc.)

C. Epidemiologic study

Brooks, Clin. Chest Med. 2:171, 1981

Component A includes the basic tests and minimal information necessary for identifying an occupational disorder. Most conscientious clinicians place great emphasis on the patient's medical history. Yet many clinicians who would never omit the family history from a thorough interview, or disregard the patient's current medication in the evaluation of a new unexplained rash will ignore or disregard that part of the patient's history dealing with one-third of the patient's life. In most charts, mention of the patient's current occupation will be omitted entirely from the medical record or will be confined to billing information.

The occupational history is an integral part of a thorough medical history, but its proper application requires a fund of knowledge and training. Without a working knowledge of occupational medicine, the occupational history is a bewildering catalog of exposures to unfamiliar chemicals. The complexity of interpreting the occupational history is discouraging to many clinicians who might otherwise incorporate it into their practice. For these reasons, an occupational history form that was devised by the American Lung Association of San Diego and Imperial Counties has been included as Figures 16 and 17.

Occupational/Environmental History Form

I. IDENTIFICATION

Name: _____ Soc. Sec. _____

Address: _____ Sex: M F

_____ Birthday: _____

Telephone: home _____ work _____

II. OCCUPATIONAL PROFILE

Fill in the table below listing all jobs at which you have worked, including short-term, seasonal, and part-time employment. Start with your present job and go back to the first. Use additional paper if necessary.

Workplace (Employer's name and address or city)	Dates worked From	To	Did you work full time?	Type of Industry (Describe)	Describe your job duties	Known health hazards in workplace (dusts, solvents, etc.)	Protective equipment used?	Were you ever off work for a health problem or injury?

Figure 16

Figure 17

III. OCCUPATIONAL EXPOSURE INVENTORY

1. Please describe any health problems or injuries you have experienced connected with your present or past jobs:
2. Have any of your co-workers also experienced health problems or injuries connected with the same jobs? ..... No Yes
   If yes, please describe:
3. Do you or have you ever smoked cigarettes, cigars, or pipes? ..... No Yes
   If so, which and how many per day:
4. Do you smoke while on the job, as a general rule? ..... No Yes
5. Do you have any allergies or allergic conditions? ..... No Yes
   If so, please describe:
6. Have you ever worked with any substance which caused you to break out in a rash? ..... No Yes
   If so, please describe your reaction and name the substance:
7. Have you ever been off work for more than a day because of an illness or injury related to work? ..... No Yes
   If so, please describe:
8. Have you ever worked at a job which caused you trouble breathing, such as cough, shortness of wind, wheezing? No Yes
   If so, please describe:
9. Have you ever changed jobs or work assignments because of any health problems or injuries? ..... No Yes
   If so, please describe:
10. Do you frequently experience pain or discomfort in your lower back or have you been under a doctor's care for back problems? ..... No Yes
    If so, please describe:
11. Have you ever worked at a job or hobby in which you came into direct contact with any of the following substances by breathing, touching, or direct exposure? If so, please check the box beside the substance.

☐ Acids	☐ Beryllium	☐ Chromates	☐ Heat (severe)	☐ Nickel	☐ Radiation	☐ Trichloroethylene
☐ Alcohols (industrial)	☐ Cadmium	☐ Coal dust	☐ Isocyanates	☐ Noise (loud)	☐ Rock dust	☐ Trinitrotoluene
☐ Alkalis	☐ Carbon tetrachloride	☐ Cold (severe)	☐ Ketones	☐ PBBs	☐ Silica powder	☐ Vibration
☐ Ammonia	☐ Chlorinated naphthalenes	☐ Dichlorobenzene	☐ Lead	☐ PCBs	☐ Solvents	☐ Vinyl chloride
☐ Arsenic	☐ Chloroform	☐ Ethylene dibromide	☐ Manganese	☐ Perchloroethylene	☐ Styrene	☐ Welding fumes
☐ Asbestos	☐ Chloroprene	☐ Ethylene dichloride	☐ Mercury	☐ Pesticides	☐ Talc	☐ X-rays
☐ Benzene		☐ Fiberglass	☐ Methylene chloride	☐ Phenol	☐ Toluene	
		☐ Halothane		☐ Phosgene	☐ TDI or MDI	

If you have answered "yes" to any of the above, please describe your exposure on a separate sheet of paper.

IV. ENVIRONMENTAL HISTORY

1. Have you ever changed your residence or home because of a health problem? ..... No Yes
   If so, please describe:
2. Do you live next door to or very near an industrial plant? ..... No Yes
   If so, please describe:
3. Do you have a hobby or craft which you do at home? ..... No Yes
   If so, please describe:
4. Does your spouse or any other household member have contact with dusts or chemicals at work or during leisure activities? ..... No Yes
   If so, please describe:
5. Do you use pesticides around your home or garden? ..... No Yes
   If so, please describe:
6. Which of the following do you have in your home? (Please check those that apply.)

   ☐ Air conditioner ☐ Air purifier ☐ Humidifier ☐ Gas stove ☐ Electric stove ☐ Fireplace ☐ Central heating

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Occupational History

Identification of asbestos exposure: Because occupational sources of exposure constitute the most frequent, heaviest and most clinically relevant exposures, a physician should start his search with the patient occupational profile or work history (Figures 16, 17). The occupational profile is a comprehensive inventory of the patient's occupation, employers and potential exposures. This part of the occupational history form is designed to serve three distinct functions. By identifying specific industries in which the patient was employed, the occupational profile raises the interviewer's index of suspicion regarding possible exposures associated with those industries. By identifying the specific job duties done by the patient, the occupational profile alerts the interviewer to specific potential hazards in the work place to which the patient has been exposed. These hazards cannot be determined merely by listing a job title. For instance, a welder may weld many different materials under very different conditions or a mechanic can have many different responsibilities in different work places. Table 21 lists common potential occupational sources of asbestos exposure. An individual patient can be exposed to asbestos in any of the occupations listed in Table 21 or, rarely, in unexpected occupations such as a laundry worker or stage hand. More cases will generally be found where large populations of workers are exposed to high levels of respirable asbestos fibers. It is therefore helpful to examine the number of workers involved in given industries, the amount of asbestos used by these industries and the opportunity for asbestos fibers to become airborne.

Most individuals are exposed to asbestos in the manufacturing industries or in trades that use asbestos containing products. The construction industry accounts for about 75 percent of the asbestos utilized in the United States, and 92 percent of this asbestos is firmly bound in the finished products, such as floor tiles, asbestos cements, roofing felts and shingles. The individuals at greatest risk from the manufacture of these products are those who handle the asbestos before it is bonded into the final product, and those individuals whose handling of the product involves sawing, filing, sanding, clipping or demolition of the dry material so that the fibers may be liberated. The remaining 8 percent of the asbestos used in the construction industry is in powder form for insulation materials, cement or acoustic tiling. These products provide a greater opportunity for asbestos fibers to become airborne.

Although shipyard use of insulation does not account for the great bulk of asbestos used, refitting processes involve the removal of old insulation in enclosed environments. This circumstance has led to high levels of asbestos fibers in the atmosphere and to a high incidence of asbestos related diseases.

Friction products such as brake linings and clutch facings contain asbestos, and exposure may occur in the installation and repair of these products. Much of this asbestos is converted to non-fibrous silicates by the heat of friction but recent studies have demonstrated 2 to 15 percent chrysotile in brake drum dust.

In the United States in 1972, only 541 individuals were employed in all known asbestos mines and mills (3). Air samples taken at these sites indicate that the hazard is greater for mill workers. Because of the small number of individuals involved, these industries will not be a major source of cases of

asbestos related disease. Although asbestiform rock deposits occur in 22 of the 50 states and miners or handlers of other mineral ores may be at risk, a hazard has not been documented. Finally, a variety of miscellaneous occupations in which exposure has been reported are also documented in Table 21.

Table 21

Sources of Occupational Exposure to Asbestos

1. Construction sites which utilize asbestos or asbestos-containing materials - lagger, painter, insulation worker, spray insulator, carpenter, mason, tile layer, demolition worker, heating equipment worker, plumber, welder, electrician, janitorial worker, sheet metal worker, and various other laborers exposed at construction sites
2. Manufacturer or distribution of asbestos-containing products (asbestos cement products, friction materials, insulation products, paper products, textiles, milling, etc.) - spinner, weaver, bag opener, cutter of dried products, carder, blender, bagger, packer, pelletizer, card loader, crusher, dryer operator, foreman, laborer, maintenance worker, mill operator, truck driver, heavy equipment operator, driller, putty manufacturing, cardboard manufacturing, automobile makers, welding rod manufacturing, munitions manufacturing, plaster makers, rubber workers
3. Shipbuilding or renovation - lagger, sailmaker-lagger, mason, painter, electrical fitter, sprayer, asbestos storemen, welder, shipfitter, plumber, driller, caulker, boilermaker, steamfitter
4. Automobile repairs - brake repairman, body repairman, mechanics, service station attendants
5. Mining, milling, transportation - driller, heavy equipment operator, truck driver, blender, bagger, packer, pelletizer, car loader, crusher, dryer operator, laboratory technician, foreman, laborer, maintenance worker, mill operator
6. Miscellaneous - repairmen, maintenance men, engineers, office workers, laboratory technicians, shipping personnel, sailors, longshoremen, dock workers, railroad workers, laundry and dry cleaning personnel, residents near asbestos processing and textile mills, persons living on or near roads where asbestos is transported, inhabitants of houses with asbestos insulation, persons living in homes with asbestos workers (spouses, etc.)

Selikoff, Asbestos and Disease, 1978
Praeger, Asbestos-Related Diseases, 1978

The second portion of the occupational history is an occupational exposure inventory (Figure 17). In this section the patient is prompted to recall specific exposures of medical significance and is asked about a few specific symptoms of particular concern or usefulness. The patient should be asked if he knows of any previous contact with asbestos or "fiber" or with asbestos containing materials such as insulation. Table 22 contains an exhaustive list of materials which contain asbestos.

Table 22

Asbestos-Containing Products

1. Building materials - pipes for gas, water and sewage; cement sheets for interior and exterior walls, reinforced asphalt or vinyl floor tiles, linoleum, panels, partitions, clapboard, asphalt siding and shingles, putties, ceiling board, millboard, stucco, plaster, artificial wood, sound proofing, facing of acoustical tile, asbestos cements, paint, roof coating and felt, caulking
2. Electrical - transformers, insulating tape, condensers, cables, spark plugs, conduits, electrical wire insulation, switch boxes, circuit breakers
3. Friction materials - gaskets, clutch plates, brakelinings, conveyor belting seals, bearing packing
4. Insulation - insulation blocks and board, pipe covering, insulation jackets, boiler and pipe covering, sprayed on structural heat insulation, pot holders, ironing board covers, table pads, stove mats, auto mufflers, automobile firewall and hood linings, glove linings
5. Miscellaneous - fire hoses, filter pads, filter paper, artificial snow, filler in rubber goods, cloth, sheets, blankets, draperies, yarn, cord, curtains, rope, twine, ribbon, welding electrodes, gas mask filters, filter cloths, catalyst supports for sulfuric acid production, steam, acid, and water proof bearings and packing, cardboard, paper products, boat hulls, airplane wings, wicks for lamps and oil burners, prison cell padding, clay for pottery and sculpture, life jackets, fireproof safety clothing, automobile undercoatings, asbestos reinforced hard standings in parking lots, asbestos asphalt, military helmet liners, piano padding, plastics, rocket reentry nose cones, frying pan handles, motion picture screens, mail bags

Selikoff, Asbestos and Disease, 1978
Praeger, Asbestos-Related Diseases, 1978

Practically, the patient should be asked if he uses any of the materials listed in Table 23 either in vocational or avocational pursuits. Interestingly, many of these materials are not labeled as containing asbestos. The purpose of the occupational exposure inventory is to prompt recall of exposure to specific agents and to more fully characterize the circumstances of exposure. In practice, both parts of the occupational history should be recorded in patients likely to have occupational diseases since serious omissions often occur when only one part is used.

Table 23

Products That May Contain Asbestos

Acoustical products	Floor tiles
Caulking material	Gaskets
Insulation materials	Paints
Paper	Plastics
Roof coatings	Roofing felts
Shingles	Textiles
Friction materials (brake linings, clutch facings)	Asbestos cement products (sheets, pipes, tiling)

Praeger, Asbestos-Related Diseases, 1978

If no exposure to asbestos is found in a detailed occupational history, and if the physician is suspicious that the disease state is related to asbestos exposure, the possibility of exposure in a non-occupational setting must be explored. This is particularly true for female patients. An occupational history should be obtained for past and present household contacts. Significant exposure occurs in household contacts presumably because asbestos laden clothing is worn and cleaned at home (186).

The environmental history segment of the form shown in Figure 17 is intended to identify certain important exposures in the home that may be clinically significant. The patient's area of residence since childhood should be listed and the presence or absence of nearby industrial plants should be determined. Mesothelioma patients without occupational exposure more frequently lived within one-half mile of such factories than did members of the control population (187). A third source of non-occupational exposure is the use of products listed in Table 22 in a non-occupational setting. Handymen who remodel their own home or other homes during their leisure time may have significant exposure. Risk is greatest if the products are sanded, cut or handled in other ways that will allow respirable asbestos fibers to be liberated.

Another source of asbestos exposure has received widespread public attention and must be mentioned, i.e. asbestos air pollution in urban areas. Asbestos fibers have been demonstrated in the vicinity of construction sites and also at random sites of air collection in New York City (188). Other

investigators have sampled air in England, Germany, Czechoslovakia, South Africa and Iceland (189). Asbestos fibers were found in the air samples of all cities tested in spite of the fact that only one city had an asbestos industry within its boundaries. These findings presumably explain the frequency with which ferruginous bodies are found in urban dwellers' lungs. No study to date has demonstrated an excess of asbestos-related disease in these individuals. The advisory committee report following the Lyon Conference in 1972 (190) expressed the opinion that there was no evidence of excess disease in the general public as a result of urban asbestos air pollution or a demonstrated risk from ingestion of fibers in water supplies.

Amount of exposure: Despite problems with estimating dose, the bulk of evidence favors a dose-response relationship for the development of asbestosis, pleural plaques and lung cancer, thus strengthening the association between asbestos exposure and these diseases. When a history of contact with asbestos is elicited, the physician should estimate the magnitude of exposure based on the onset of exposure, the number of years of exposure, the circumstances of exposure, dust control measures the patient employed and visible dust in the environment. Table 24 lists factors favoring heavy asbestos exposure.

Table 24

Factors Determining Heavy Asbestos Exposure

1. Exposure before 1950
2. Constant exposure to high levels
3. Long-term exposure
4. Lack of use of protective inhalation devices
5. Occupations receiving high asbestos exposure
   a. Asbestos mill workers
   b. Asbestos textile factory workers
   c. Sprayers using asbestos insulation
   d. Asbestos insulation laggers
   e. Asbestos bag openers
   f. Demolition workers
   g. Ship refitters

Praeger, Asbestos-Related Diseases, 1978

The amount of time elapsed since initial exposure is important for two reasons. Most of the consequences of asbestos exposure have a long latency period. Also, the level of exposure in the 1930 to 1950 period, before effective dust control measures were introduced or enforced, was often high. The number of years of exposure, combined with the measured or estimated asbestos fiber or dust particle levels, gives a general estimate of the magnitude of exposure which is shown by epidemiologic studies to be related to the prevalence and extent of disease in the exposed population.

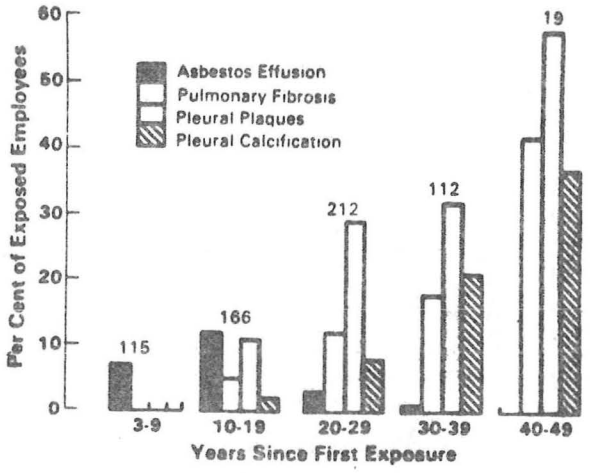
Although visibile dust particles are much larger than particles of respirable size, there is a rough correlation between the visible dust levels and the concentration of invisible respirable particles. Thus visible dust can be used as a crude indication of previous exposure levels in environments where airborne asbestos fibers are known to have existed.

Finally, various epidemiologic studies have demonstrated that persons in the occupations listed in Table 24 have had heavy exposure and a significant excess of asbestos-related disease. Even though dust control measures and protective equipment have been widely used in recent years, the majority of patients now being seen were exposed before these measures were introduced.

Dose-response relationships are also useful in determining whether non-specific disease presentations such as pleural effusions or interstitial fibrosis are likely related to asbestos exposure. As shown in Figure 18 asbestosis, pleural plaques, lung cancer and mesothelioma, usually have latent periods of 20 years or more, whereas a benign effusion could be observed during the first 20 years after exposure. Additionally, the prognosis of the patient, along with recommendations concerning future employment, will be based on the physician's estimation of past exposure and how much future dust exposure will add to the total dust burden already encountered.

Figure 18

Time Course of Asbestos-Related Disease



Gaensler, N. Engl. J. Med. 307:107, 1982

Initial Diagnostic Studies

A physical examination may not be helpful. However, the presence of basal rales in an asbestos worker is an important finding. Clubbing of the fingers as a manifestation of asbestosis, evidence suggesting pleural disease in suspected mesothelioma and unilateral wheeze in a patient who might have lung cancer are additional findings of importance.

Interpretation of a properly taken chest X-ray is crucial for making a diagnosis. In general, it is not possible to make a clinical diagnosis of pneumoconiosis without a positive chest X-ray. This is not to say that symptomatic individuals who are exposed to asbestos and have negative chest X-rays could not have asbestosis. However, unless pathological lung biopsy material is available, one is hard pressed to make an definitive diagnosis of asbestos-related lung disease when the X-ray film is negative. Since conventional chest radiography plays an important part in the investigation and diagnosis of asbestos related diseases, it is critical that the chest radiograph be of high quality. The chest radiograph must include the entire thorax from the lung apices to just below the costophrenic angles. Adequate viewing of the lateral chest wall is essential if pleural lesions are not to be overlooked. A routine posteroanterior and lateral chest film should be supplemented by 45 degree oblique views of both sides of the chest. These film will allow the majority of pleural lesions to be profiled tangentially and thus seen at their maximum radiodensity. Computerized tomography has the ability to demonstrate plaques at an earlier stage than chest radiographs and the characteristic pleural lesions of mesothelioma are easily defined by computerized tomographic scanning of the lung fields. Interstitial fibrosis may also be shown at an earlier stage using this technique. In the vast majority of cases, however, the chest film is perfectly adequate and computerized tomography should be reserved for special situations in view of the cost involved in its use at the present.

Pulmonary function studies are helpful in evaluating both the presence and extent of pulmonary impairment. Simple spirometry should be performed in all patients suspected of having asbestos-related pulmonary diseases. Finding a restricted pattern is quite useful. Problems, however, arise when differentiating spirometric changes due to cigarette smoking from those due to occupational exposures. Generally, significant obstructive airways disease does not occur as the result of chronic inhalation of asbestos. If the FEV_1/FVC is less than 55 percent, it is probably not due to inhalation of asbestos, but rather to some other cause, such as chronic bronchitis or emphysema from cigarette smoking, or reversible airways disease of occupational or non-occupational origin. Small changes in FEV_1 and FEV_1/FVC can occur in some patients but the changes are small and disability does not occur (58).

If significant airway obstruction is present it is difficult to accurately interpret the spirogram for restrictive disease, since the FVC is also decreased in many instances. The decreased FVC is accompanied by an increased functional residual capacity and residual volume leading to a normal or elevated total lung capacity. Restrictive lung disease is generally associated with reduction of all lung volumes. Thus, when significant airway obstruction is present, specific tests measuring functional residual capacity and total lung capacity are indicated.

Special laboratory investigations are indicated for specific reasons and are not necessary for all evaluations. Thoracentesis with laboratory studies as outlined in the previous section should be performed in any instance where pleural effusion is present. Fiber-optic bronchoscopy may be required in those instances in which bronchogenic carcinoma is suspected. Further, identification of specific materials in biological fluids or tissue may be necessary in certain specific instances as outlined earlier.

Epidemiologic Study

In some situations, particularly in the case when environmental concentrations of a material in question are said to be at a safe level, or evidence of asbestos related dieseases are present in an environment not thought to be at risk, study of a population of workers may be necessary to better determine the presence or absence of an occupational pulmonary hazard. In such cases, epidemiologic studies might be indicated to confirm the presence or absence of a pulmonary health hazard. While the average physician does not have the necessary resources to perform such studies, since the practicing physician is often the first to suspect an occupational health problem, it behooves the physician to report his or her observations to those professionals who can investigate these problems further.

THE "WORRIED WELL"

As the general public has become more aware of the hazards of asbestos exposure, the clinician has been called upon more frequently to evaluate patients who have been exposed to asbestos but who have minimal or no symptoms. What signs of early asbestos effects should be sought in an individual with no obvious evidence of disease?

A complete medical history and physical examination with special attention directed towards the cardiorespiratory and gastrointestinal systems should be performed. On physical examination, basilar crepitation in two or more locations is the earliest sign. The earliest radiographic findings are small, irregular densities that favor both lung bases; if present in a profusion greater than 1/0 on the ILO/UC classification, the suspicion of early asbestos effect should be high. The presence of small irregular opacities increases with age and cigarette smoking without asbestos exposure (191) however, so undue emphasis should not be placed on low grade opacities as an isolated finding in elderly cigarette smokers.

Pulmonary function studies, including spirometry and a diffusing capacity should be obtained in all of these patients. Pulmonary diffusing capacity has been shown in several studies to be abnormal in some asbestos workers before other functional, radiographic or clinical abnormalities appear and it is invariably reduced in advanced asbestosis. Other studies have detected changes in the lungs mechanical properties, specifically a decrease in compliance and an increase in calculated upstream resistance in those asymptomatic patients with heavy dust exposure (58, 192). Similar results have been obtained in a subsequent study using the closing volume test.

Many factors other than asbestos dust exposure affect both pulmonary diffusing capacity, (infiltrative lung diseases, pulmonary vascular abnormalities, widespread pulmonary emphysema, cigarette smoking) and abnormalities of airway function (bronchitis or asthma). Therefore, an isolated abnormality on either test in a given individual is not of specific diagnostic value. Caution should be used in interpreting mild reductions in total lung capacity, vital capacity and FEV_1 in black asbestos workers, since previous studies have demonstrated important ethnic differences in the relations of lung function to age and height with black persons having smaller volumes or maximal flows by about 13 percent (193). Repeated observations showing progressive decline unexplained by other disease processes, coupled with information concerning dust exposure, enhance the suspicion that these abnormalities are related to asbestos exposure. The practical significance of these functional abnormalities remains to be shown, since: 1) it is not known whether what is detected is, in fact, the beginning of a process that will ultimately lead to asbestos-related pulmonary disease; and 2) it is not known whether intervention, such as removal from exposure, would prevent the ultimate development of disease.

Various authors have compared the value of clinical examination, radiographic studies and pulmonary function studies in the detection of early asbestos effect on the lung (32, 42, 44, 51, 194-196), but in an individual case, any one of these methods may be the first to reveal abnormalities. Therefore, all three should be obtained, with repeated observations at a later date if the significant detected abnormalities are unclear.

Individuals with no significant history of asbestos exposure and no evidence on pulmonary function studies or chest X-rays of early manifestations of asbestos-related disease should be reassured of this fact and follow-up based on their age and the presence of other medical conditions. For those patients with a history of substantial exposure but without evidence of early asbestos effect, regularly scheduled visits spaced at one to two year intervals should be instituted. These patients should be reassured that no abnormalities have been found. If the patient is returning to the same work environment in which he was exposed, evaluation of the environment in terms of dust levels and control measures should be made to ensure minimal exposure in the future. Minimal exposure should mean less than two fibers per milliliter of air.

Individuals with findings on examination, chest X-ray or pulmonary function studies that are consistent with early asbestos effect should be followed no less frequently than at one year intervals, especially if they are still working in the environment that caused their exposure. Evaluation of asbestos fiber levels in the environment must be made to ensure minimal future exposure. If the dust levels are uncontrolled, the physician should recommend that the individual switch to a different job even though it has not been demonstrated that removal from exposure will be followed by regression of changes noted. However, if past exposure has been heavy and subsequent institution of dust control measures have reduced the likelihood of significant future exposure before the worker retires, the individual may be allowed to continue employment since future exposure will contribute a small part of the total dose of fiber. All workers in an environment where asbestos exposure occurs should be strongly encouraged to discontinue cigarette smoking.

EPILOGUE

"When you come to a patient's house, you should ask him what sort of pains he has, what caused them and how many days he has been ill, whether the bowels are working and what sort of food he eats", so says Hippocrates in his work, *Affections*. I may venture to ask one more question: What occupation does he follow? Though this question may be concerned with the exciting causes yet I regard it as well timed or rather indispensable and it should be particularly kept in mind when the patient to be treated belongs to the common people. In medical practice, however, I find that attention is hardly ever paid to this matter, or if the doctor in attendance knows it without asking, he gives little heed to it, though for effective treatment, evidence of this sort has the utmost weight. Wherefore do you kind reader, give a friendly reception to my treatise which, though no great work of art, was written for the good of the community, or at all events for the benefit and comfort of the working classes.

Bernardini Ramazzini
DeMorbus Artificium Diatriba, 1713

BIBLIOGRAPHY

1. New York Times, August 27, 1982.

2. Wilson, J. G.: The addition of talc and asbestos to pat clay by part and present inhabitants of Karamoja District in Uganda and Kenya. Man 8:300, 1973.

3. Selikoff, I. J., and D. H. K. Lee: Asbestos and disease. New York, Academic Press, 1978.

4. Gilson, J. C.: Asbestos cancer: Past and future hazards. Proc. Roy. Soc. Med. 66:395, 1973.

5. Becklake, M. R.: Asbestos related diseases of the lung and other organs: Their epidemiology and implications for clinical practice. Am. Rev. Respir. Dis. 114:187, 1976.

6. Levine, R. J., ed: Asbestos: An information resource. Bethesda, Maryland, National Cancer Institute (USDHEW) No. 791681, 1978.

7. Cooke, W. E.: Fibrosis of the lungs due to the inhalation of asbestos dust. Br. Med. J. 2:147, 1924.

8. Lynch, J. M., and W. A. Smith: Pulmonary asbestosis: Carcinoma of the lung in asbesto-silicosis. Am. J. Cancer 24:56, 1935.

9. Klemperer, P., and C. B. Rabin: Primary neoplasms of the pleura. Arch. Pathol. Lab. Med. 11:385, 1931.

10. Weiss, A.: Pleurakrebs bei Lungenasbestose, in vivo morphologisch Gesichert. Medizinische 3:93, 1953.

11. Leichner, F.: Primary mesothelial-cell tumor of the peritoneum in asbestosis. Arch. Gewerbepathol. Gewerbehyg. 13:382, 1954.

12. Wagner, J. C., C. A. Sleggs, and P. Marchand: Diffuse pleural mesothelioma and asbestos exposure in Northwestern Cape Province. Br. J. Ind. Med. 17:260, 1960.

13. Stanton, M. F., M. Layard, A. Tegeris, et al.: Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimension. Natl. Cancer Inst. Monogr. 58:587, 1977.

14. Health and Safety Executive, Asbestos Final Report of the Advisory Committee. London, Her Majesty's Stationery Office, 1979.

15. Anderson, H., R. Lilis, S. Daum, et al.: Household exposure to asbestos and risk of subsequent disease. In: Lemen, R. A., and J. M. Dement, eds.: Dust and Disease. Park Forest South, Illinois, Pathotox Publishers, 1979.

16. Parkes, W. R.: Asbestos-related disorders. Br. J. Dis. Chest 67:261, 1973.

17. British Occupational Hygiene Society, Committee on Hygiene Standards: Hygiene standard for chrysotile asbestos dust. Ann. Occup. Hyg. 11:47, 1968.

18. Berry, G., J. C. Gilson, S. Holmes, et al.: Asbestosis: A study of dose-response in an asbestos textile factory. Br. J. Ind. Med. 36:98, 1979.

19. Peto, J.: The hygiene standard for chrysotile asbestos. Lancet 1:484, 1978.

20. Hammond, E. C., I. J. Selikoff, and H. Seidman: Asbestos exposure, cigarette smoking and death rates. Ann. N. Y. Acad. Sci. 330:473, 1979.

21. McMillan, G. H. G., R. J. Pethybridge, and G. Sheers: Effect of smoking on attack rates of pulmonary and pleural lesions related to exposure to asbestos dust. Br. J. Ind. Med. 37:268, 1980.

22. Weiss, W.: Cigarette smoking, asbestos and pulmonary fibrosis. Am. Rev. Respir. Dis. 104:223, 1971.

23. Weiss, W., and P. A. Theodus: Pleuropulmonary disease among asbestos workers in relation to smoking and type of exposure. J. Occup. Med. 20:341, 1978.

24. Selikoff, I. J. and E. C. Hammond: Asbestos and smoking. J.A.M.A. 242:458, 1979.

25. Casey, K. R., W. N. Rom, and F. Moatamed: Asbestos-related diseases. Clin. Chest Med. 2:179, 1981.

26. Smither, W. J.: Secular changes in asbestos in an asbestos factory. Ann. N. Y. Acad. Sci. 132:166, 1965.

27. Hunter, D.: The Diseases of Occupations, English University Press, London, England, pp. 877, 1955.

28. Wyers, H.: Asbestosis. Post. Med. J. 25:631, 1949.

29. Thomson, M. L., M. W. McGrath, W. J. Smither, et al.: Some anamolies in the measurement of pulmonary diffusion in asbestosis and chronic bronchitis with emphysema. Clin. Sci. 21:1, 1961.

30. Doll, N. J., R. P. Stankus, and H. W. Barkman: Immunopathogenesis of asbestosis, silicosis and coal worker's pneumoconiosis. Clin. Chest Med. 4:3, 1983.

31. Turner-Warwick, M., and W. R. Parkes: Circulating rheumatoid and anti-nuclear factors in asbestos workers. Br. Med. J. 2:429, 1970.

32. Williams, R., and P. Hugh-Jones: The significance of lung function changes in asbestosis. Thorax 15:109, 1960.

33. Richards, A. G., and G. M. Barrett: Rheumatoid lung changes associated with asbestosis. Thorax 13:185, 1958.

34. Bartsch, P., J. Salmon, and P. Mahieu: Asbestosis and systemic lupus eruthematosus. Int. Arch. Allergy Appl. Immunol. 61:28, 1980.

35. Gerber, M. A.: Asbestosis and neoplastic disorders of the hematopoietic system. Am. J. Clin. Pathol. 53:204, 1970.

36. Kagan, E., R. J. Jacobson, K. Y. Yeung, et al.: Asbestos-associated neoplasms of B-cell lineage. Am. J. Med. 67:325, 1979.

37. Lieben, J.: Malignancies in asbestos workers: Arch. Environ. Health 13:619, 1966.

38. Gaumer, H. R., N. J. Doll, J. Kaimal, et al.: Diminished suppressor cell function in patients with asbestosis. Clin. Exp. Immunol. 44:108, 1981.

39. Soutar, C. A., G. Simon, and M. Turner-Warwick: The radiology of asbestos-induced disease of the lung. Br. J. Dis. Chest 68:235, 1974.

40. Solomon, A.: The radiology of asbestosis. S. Afr. Med. J. 43:847, 1969.

41. Hurwitz, M.: Roentgenologic aspects of asbestosis. Am. J. Roentgenol. 85:256, 1961.

42. Leathart, G. L.: Clinical, bronchographic, radiological and physiological observations in ten cases of asbestosis. Br. J. Ind. Med. 17:213, 1960.

43. UICC/Cincinnati classification of the radiographic appearances of pneumoconiosis. Chest 58:57, 1970.

44. Weil, H., C. Waggenspack, and W. Bailey: Radiographic and physiologic patterns amongst workers engaged in manufacture of asbestos cement products. J. Occup. Med. 15:248, 1973.

45. Greaves, I. A.: Rheumatoid "pneumoconiosis" (Caplan's syndrome) in an asbestos worker: A 17 years' follow-up. Thorax 34:404, 1979.

46. Turner-Warwick, M.: A perspective view on widespread pulmonary fibrosis. Br. Med. J. 2:371, 1974.

47. Schneider, H. J., B. Felson, and L. L. Gonzales: Rounded atelectesis. Am. J. Roentgenol. 134:225, 1980.

48. Hanke, R., and R. Kretzschmar: Round atelectesis. Semin. Roentgenol. 15:174, 1980.

49. Solomon, A.: The radiology of asbestos-related disease with special reference to diffuse mesothelioma. Semin. Oncol. 8:290, 1981.

50. Bjure, J., B. Soderholm, and J. Widimsky: Cardiopulmonary function studies in workers dealing with asbestos and glasswool. Thorax 19:22, 1964.

51. Leathart, G. L.: Pulmonary function tests in asbestos workers. Trans. Soc. Occup. Med. 18:49, 1968.

52. Lebowitz, M.: Occupational exposures in relation to symptomatology and lung function in a community population. Environ. Res. 14:59, 1977.

53. McDonald, J. C., M. R. Becklake, G. Fournier-Massey, et al.: Respiratory symptoms in chrysotile asbestos mine and mill workers of Quebec. Arch. Environ. Health 24:358, 1972.

54. Muldoon, B. C., and M. Turner-Warwick: Lung function studies in asbestos workers. Br. J. Dis. Chest 66:121, 1972.

55. Harless, K. W., S. Watanabe, and A. D. Renzetti: The acute effects of chrysotile asbestos exposure on lung function. Environ. Res. 16:360, 1978.

56. Rodriquez-Roisin, R., J. E. M. Merchant, G. M. Cochrane, et al.: Maximal expiratory flow-volume curves in workers exposed to asbestos. Respiration 39:158, 1980.

57. Murphy, R. L. H., E. A. Gaensler, R. A. Redding, et al.: Low exposure to asbestos. Arch. Environ. Health 25:253, 1972.

58. Begin, R., A. Cantin, M. E. Berthiau, et al.: Airway function in lifetime nonsmoking older asbestos workers. Am. J. Med. 75:631, 1983.

59. Craighead, J. E.: The pathology of asbestos-associated diseases of the lungs and pleural cavities: Diagnostic criteria and proposed grading schema. Arch. Pathol. Lab. Med. 106:544, 1982.

60. Churg, A., and J. Golden: Current problems in the pathology of asbestos-related disease. Pathol. Annu. 17:33, 1982.

61. Schoenberger, C. I., G. W. Hunninghake, O. Kawanami, et al.: Role of alveolar macrophages in asbestosis: Modulation of neutrophil migration to the lung after acute asbestos exposure. Thorax 37:803, 1982.

62. Corrin, B., and A. B. Price: Electron microscopic studies in desquamative interstitial pneumonia associated with asbestos. Thorax 27:324, 1972.

63. Scadding, J. G., and K. F. W. Hinson: Diffuse fibrosing alveolitis (diffuse interstitial fibrosis of the lungs). Thorax 22:291, 1967.

64. Gaensler, E. A., C. B. Carrington, R. E. Coutu, et al.: Pathological, physiological, and radiological correlations in the pneumoconioses. Ann. N. Y. Acad. Sci. 200:574, 1972.

65. Hourihane, D. O'B., and W. T. E. McCaughey: Pathological aspects of asbestosis. Postgrad. Med. J. 42:613, 1966.

66. Thomson, J. G., R. O. C. Kaschula, and R. R. MacDonald: Asbestos as a modern urban hazard. S. Afr. J. Med. 37:77, 1963.

67. Churg, A.: Fiber counting and analysis in the diagnosis of asbestos-related disease. Hum. Pathol. 14:381, 1982.

68. Gross, P., L. J. Cralley, and R. T. P. deTreville: "Asbestos" bodies: Their nonspecificity. Am. Ind. Hyg. Assoc. J. 28:541, 1967.

69. Sebastien, P., A. Gaudichet, J. Bignon, et al.: Zeolite bodies in human lungs from Turkey. Lab. Invest. 44:420, 1981.

70. Roggli, V. L., and P. C. Pratt: Relationship of numbers of asbestos bodies on iron-stained tissue sections and asbestos body counts in lung tissue digests. Hum. Pathol. (In Press)

71. Pooley, F. D.: Asbestos bodies: Their formation, composition and character. Environ. Res. 5:363, 1972.

72. Botham, S. K., and P. F. Holt: Development of asbestos bodies on amosite, chrysotile and crocidolite fibres in guinea pig lungs. J. Pathol. 105: 159, 1971.

73. Miller, A., A. M. Langer, A. S. Tierstein, et al.: "Nonspecific" interstitial pulmonary fibrosis--Association with asbestos fibers detected by electron microscopy. N. Engl. J. Med. 292:91, 1975.

74. Davies, P., A. C. Allison, J. Ackerman, et al.: Asbestos induces selective release of lysosomal enzymes from mononuclear phagocytes. Nature 251:423, 1974.

75. Davies, P., and A. C. Allison: Secretion of macrophages enzymes in relation to the pathogenesis of chronic inflammation. In: Nelson, D. S., ed.: Immunobiology of the Macrophage. New York, Academic Press, 1976, pp. 427.

76. Karnovsky, M. L., and J. K. Lazdens: Biochemical criteria for activated macrophages. J. Immunol. 121:809, 1978.

77. Schoenberger, C., G. Hunninghake, J. Gadek, et al.: Inflammation and asbestosis: Characterization and maintenance of alveolitis following acute asbestos exposure. Chest 80(Suppl):705, 1981.

78. Bitterman, P., S. Rennard, C. Schoenberger, et al.: Asbestos stimulates alveolar macrophages to release a factor causing human lung fibroblasts to replicate. Chest 80(Suppl):385, 1981.

79. Allison, A. C.: Mechanisms of macrophage damage in relation to the pathogenesis of some lung diseases. In: Brain, J. D., Proctor, D. F., and Reid, L. M., eds.: Respiratory Defense Mechanisms, Part II. New York, Marcel Dekker, 1975, pp. 1075.

80. Hasselbacher, P.: Binding of immunoglobulin and activation of complement by asbestos fibers. J. Allergy Clin. Immunol. 64:294, 1979.

81. Wilson, M. R., H. G., Gaumer, and J. E. Salvaggio: Activation of the alternative pathway and generation of chemotactic factors by asbestos. J. Allergy Clin. Immunol. 60:218, 1977.

82. Hunninghake, G. W., J. E. Gadek, H. M. Fales, et al.: Human alveolar macrophage-derived chemotactic factor for neutrophils: Stimuli and partial characterization. J. Clin. Invest. 66:473, 1980.

83. Keogh, B., B. Line, M. Rust, et al.: Clinical staging of patients with idiopathic pulmonary fibrosis. Am. Rev. Respir. Dis. 123(Part 2):89, 1981.

84. Gadek, J. E., J. A. Kelman, G. Fells, et al.: Collagenase in the lower respiratory tract of patients with idiopathic pulmonary fibrosis. N. Engl. J. Med. 301:737, 1979.

85. Werb, Z., and S. Gorden: Elastase secretion by stimulated macrophages. Characterization and regulation. J. Exp. Med. 142:361, 1975.

86. White, R., H. S. Lin, and C. Kuhn: Elastase secretion by peritoneal exudate cells and alveolar macrophages. J. Exp. Med. 146:802, 1977.

87. Gadek, J. E., G. Hunninghake, G. A. Fells, et al.: Production of connective tissue specific proteases by human alveolar macrophages is constitutive. (nonregulable). Am. Rev. Respir. Dis. 123(Part 2):224, 1981.

88. Hoidal, J. R., G. D. Beall, and J. E. Repine: Production of hydroxyl radical by human alveolar macrophages. Infect. Immun. 26:1088, 1979.

89. Hoidal, J. R., R. B. Fox, P. A. LaMarbe, et al.: Altered oxidative metabolic responses *in vitro* of alveolar macrophages from asymptomatic cigarette smokers. Am. Rev. Respir. Dis. 123:85, 1981.

90. Nathan, C. F., L. H. Bruckner, S. C. Silverstein, et al.: Extracellular cytolysis by activated macrophages and granulocytes. I. Pharmacologic triggering of effector cells and the release of hydrogen peroxide. J. Exp. Med. 149:84, 1979.

91. Miller, K., and E. Kagan: The *in vivo* effects of asbestos on macrophage membrane structure and population characteristics--a scanning electron microscope study. J. Reticuloendothel. Soc. 20:159, 1976.

92. Miller, K., and E. Kagan: Immune adherence reactivity of rat alveolar macrophages following inhalation of crocidolite asbestos. Clin. Exp. Immunol. 29:152, 1977.

93. Miller, K., Z. Weintraub, and E. Kagan: Manifestations of cellular immunity in the rat after prolonged asbestos exposure. I. Physical interaction between alveolar macrophages and splenic lymphocytes. J. Immunol. 123:1029, 1979.

94. Masih, N., J. Majesha, and T. Yoshida: Studies on experimental pulmonary granulomas. I. Detection of lymphokines in granulomatous lesions. Am. J. Pathol. 95:391, 1979.

95. Scadding, J. G.: Diffuse pulmonary alveolar fibrosis. Thorax 29:271, 1974.

96. Gaensler, E. A., M. V. B. Moister, and J. Hamm: Open-lung biopsy in diffuse pulmonary disease. N. Engl. J. Med. 270:1319, 1964.

97. Spencer, H.: Interstitial pneumonia. Annu. Rev. Med. 18:423, 1967.

98. Brody, A. R., and J. E. Craighead: Interstitial associations of cells lining air spaces in human pulmonary fibrosis. Virchows Arch. Abt. A. Pathol. Anat. 372:39, 1976.

99. Pledger, W. J., H. N. Stiles, H. N. Antoniades, et al.: An ordered sequence of events is required before BALB/C-3T3 cells became committed to DNA synthesis. Proc. Natl. Acad. Sci. USA 75:2839, 1978.

100. Bitterman, P. B., S. Adelberg, and R. G. Crystal: Mechanisms of pulmonary fibrosis-spontaneous release of the alveolar macrophage-derived growth factor in the interstitial lung disorders. J. Clin. Invest. 72:1801, 1983.

101. Bitterman, P. B., S. I. Rennard, S. Adelberg, et al.: Role of fibronectin as a growth factor for fibroblasts. J. Cell Biol. 1983. (In Press)

102. Bitterman, P. B., S. Rennard, B. Koegh, et al.: Chronic alveolar macrophage release of fibronectin and alveolar macrophage-derived growth factor correlates with functional deterioration in fibrotic lung disease. Clin. Res. 31:414a. (Abstract)

103. Postlethwaite, A. E., R. Snyderman, and A. H. Kang: The chemotactic attraction of human fibroblasts to a lymphocyte-derived factor. J. Exp. Med. 144:1188, 1976.

104. Wahl, S. M., L. M. Wahl, and W. Y. MacCarthy: Lymphocyte-mediated activation of fibroblast proliferation and collagen production. J. Immunol. 121:942, 1978.

105. Lemaire, I., and M. Rola-Pleszczynski: Production of human lung fibroblast activating factor in mixed lymphocyte cultures. Clin. Res. 28:688A, 1980.

106. Heppleston, A. G., and J. A. Styles: Activity of a macrophage factor in collagen formation by silica. Nature (Lond.) 214:521, 1967.

107. Harrington, J. S., M. Ritchie, P. C. King, et al.: The *in vitro* effects of silica treated hamster macrophages or collagen production by hamster fibroblasts. J. Pathol. 109:21, 1973.

108. Nourse, L. D., P. N. Nourse, H. Botes, et al.: The effects of macrophages isolated from the lungs of guinea pigs dusted with silica on collagen biosynthesis by guinea pig fibroblasts in cell culture. Environ. Res. 9:115, 1975.

109. Reiser, K. M., and J. A. Last: Silicosis and fibrogenesis: Fact and artifact. Toxicology 13:51, 1979.

110. Buchanan, W. D.: Asbestosis and primary intrathoracic neoplasms. Ann. N. Y. Acad. Sci., 132:507, 1965.

111. Bitterman, P. B., S. I. Rennard, and R. G. Crystal: Environmental lung disease and the interstitium. Clin. Chest Med. 2:393, 1981.

112. Anthonisen, N. R.: Long term oxygen therapy. Ann. Intern. Med. 99:519, 1983.

113. Selikoff, I. J., R. A. Bader, M. E. Bader, et al.: Asbestosis and neoplasia. Am. J. Med. 42:487, 1967.

114. Eisenstadt, H. B.: Asbestos pleurisy. Dis. Chest 46:78, 1964.

115. Eisenstadt, H. B.: Pleural effusions in asbestosis. N. Engl. J. Med. 290:1025, 1974.

116. Gaensler, E. A., and A. I. Kaplan: Asbestos pleural effusion. Ann. Intern. Med. 74:178, 1971.

117. Sluis-Cremer, G. K., and I. Webster: Acute pleurisy in asbestos exposed persons. Environ. Res. 5:380, 1972.

118. Wright, P. H., A. Hanson, L. Kreel, et al.: Respiratory function changes after asbestos pleurisy. Thorax 35:31, 1980.

119. Weiss, W., R. Levin, and L. Goodman: Pleural plaques and cigarette smoking in asbestos workers. J. Occup. Med. 23:427, 1981.

120. Harries, P. G., F. A. F. Mackenzie, G. Sheers, et al.: Radiological survey of men exposed to asbestos in naval dockyards. Br. J. Ind. Med. 29:274, 1972.

121. Meurman, L.: Asbestos bodies and pleural plaques in a Finnish series of autopsy cases. Acta. Pathol. Microbiol. Scand. 181(Suppl):1, 1966.

122. Hillerdal, G.: Pleural plaques in a health survey material: Frequency, development and exposure to asbestos. Scand. J. Respir. Dis. 59:257, 1978.

123. Becklake, M. R., G. G. Fournier-Massey, J. C. McDonald, et al.: Lung function in relation to chest radiographic changes in Quebec asbestos workers. Bull. Physiopathol. Respir. (Nancy) 6:637, 1970.

124. Fletcher, D. E.: A mortality study of shipyard workers with pleural plaques. Br. J. Ind. Med. 29:142, 1972.

125. Hourihane, D. O'B., L. Lessof, and P. C. Richardson: Hyaline and calcified pleural plaques as an index of exposure to asbestos: A study of radiological and pathological features of 100 cases with a consideration of epidemiology. Br. Med. J. 1:1069, 1966.

126. Sargent, E. N., G. Jacobson, and J. S. Gordonson: Pleural plaques: A signpost of asbestos dust inhalation. Semin. Roentgenol. 12:287, 1977.

127. Mattson, S. B., and T. Ringqvist: Pleural plaques and exposure to asbestos. Scand. J. Respir. Dis. 75(Suppl):4, 1970.

128. Roberts, G. H.: The pathology of parietal pleural plaques. J. Clin. Pathol. 24:348, 1971.

129. Hillerdal, G.: The pathogenesis of pleural plaques and pulmonary asbestosis: Possibilities and impossibilities. Eur. J. Respir. Dis. 61:129, 1980.

130. Navratil, M., and J. Dobias: Development of pleural hyalinosis in long term studies of persons exposed to asbestos dust. Environ. Res. 6:455, 1973.

131. Lynch, K. M., and W. A. Smith: Pulmonary asbestosis. III. Carcinoma of lung in asbestos-silicosis. Am. J. Cancer 24:56, 1935.

132. Doll, R.: Mortality from lung cancer in asbestos workers. Br. J. Ind. Med. 12:81, 1955.

133. Lemen, R. A., J. M. Dement, and J. K. Wagoner: Epidemiology of asbestos-related diseases. Environ. Health Perspect. 34:1, 1980.

134. McDonald, J. C.: Asbestos and lung cancer: Has the case been proven? Chest 78(Suppl):374, 1980.

135. Selikoff, I. J., E. C. Hammond, and H. Seidman: Mortality experience of insulation workers in the United States and Canada 1943-1976. Ann. N. Y. Acad. Sci. 330:91, 1979.

136. Sluid-Cremer, G. K.: The relationship between asbestosis and bronchial cancer. Chest 78(Suppl):380, 1980.

137. Becklake, M. R.: Environmental exposure to asbestos: A factor in the rising rate of cancer in the industrialized world? (Editorial). Chest 76:245, 1979.

138. Saracci, R.: Asbestos and lung cancer: An analysis of the epidemiological evidence on the asbestos-smoking interaction. Int. J. Cancer 20:323, 1977.

139. Hourihane, D. O'B., and W. T. E. McCaughey: Pathological aspects of asbestosis. Postgrad. Med. J. 42:613, 1966.

140. Kannerstein, M., and J. Churg: Pathology of carcinoma of the lung associated with asbestos exposure. Cancer 30:14, 1972.

141. Whitwell, F., M. L. Newhouse, and D. R. Bennett: A study of the histological cell types of lung cancer in workers suffering from asbestosis in the United Kingdom. Br. Ind. Med. 31:298, 1974.

142. Hueper, W. C.: Occupational and environmental cancer of the respiratory tract. Recent Results in Cancer Research, Volume 3, Berlin, Springler, 1966.

143. Warnock, M. L., and A. M. Churg: Association of asbestos in bronchogenic carcinoma in a population with low asbestos exposure. Cancer 35:1236, 1975.

144. Vincent, R. G., J. W. Pickrin, W. W. Lane, et al.: The changing histopathology of lung cancer. A review of 1682 cases. Cancer 39:1647, 1977.

145. Fontana, R. A.: Early diagnosis of lung cancer. Am. Rev. Respir. Dis. 116:399, 1977.

146. Berenblum, I.: Irritation and carcinogenesis. Arch. Pathol. 38:233, 1944.

147. Heidelberger, C.: Studies on the mechanisms of carcinogenesis by polycyclic aromatic hydrocarbons and their derivatives. In: Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism, and Carcinogenesis R. I. Freudenthal, and P. W. Jones, Eds., Volume 1, Raven Press, New York, page 1, 1976.

148. Marx, J. L.: Tumor promoters: Carcinogenesis gets more complicated. Science 201:515, 1978.

149. Sivak, A., B. T. Mossman, and B. L. Van Duuren: Activation of cell membrane enzymes in the stimulation of cell division. Biochem. Biophys. Res. Commun. 46:605, 1972.

150. Mossman, B. T., J. E. Craighead, and B. V. MacPherson: Asbestos-induced epithelial changes in organ cultures of hamster trachea: Inhibition by retinyl methyl ether. Science 207:311, 1980.

151. Mossman, B. T., P. A. Halleron, and J. E. Craighead: Stimulation of Na^+ -K^+ ATPase activity in tracheal epithelial cells after exposure to crocidolite asbestos. J. Cell Biol 83:288a, 1979.

152. Antman, K. H.: Malignant mesothelioma. N. Engl. J. Med. 303:200, 1980.

153. Antman, K. H.: Clinical presentation and natural history of benign and malignant mesothelioma. Semin. Oncol. 8:313, 1981.

154. Legha, S. S., and F. M. Muggia: Pleural mesothelioma: Clinical features and therapeutic implication. Ann. Intern. Med. 87:618, 1977.

155. Chahinian, A. P., T. F. Pajek, J. F. Holland, et al.: Diffuse malignant mesothelioma: Prospective evaluation of 69 patients. Ann. Intern. Med. 97:746, 1982.

156. Roberts, G. H.: Diffuse pleural mesothelioma. A clinical pathological study. Br. J. Dis. Chest 64:201, 1970.

157. Cantarone, G., C. Ridofi, L. Savelli, et al.: Pleural mesothelioma: a slowly progressive case. Minerva Med. 66:1300, 1975.

158. Ratzer, E. R., J. L. Pool, and M. R. Melamed: Pleural mesotheliomas: Clinical experiences with thirty-seven patients. Am. J. Roentgenol. 99:863, 1967.

159. Whitewell, F., and R. M. Rawcliffe: Diffuse malignant pleural mesothelioma and asbestos exposure. Thorax 26:6, 1971.

160. Sleggs, C. A., P. Marchand, and J. C. Wagner: Diffuse pleural mesothelioma in South Africa. S. Afr. Med. J. 35:28, 1961.

161. Taryle, D. A., S. Lakshminarayan, and S. A. Sahn: Pleural mesotheliomas. An analysis of 18 cases and review of the literature. Medicine (Baltimore) 55:153, 1976.

162. Heller, R. M., M. L. Janower, and A. L. Weber: The radiological manifestations of malignant pleural mesothelioma. Am. J. Roentgenol. 108:53, 1970.

163. Solomon, A.: Radiological features of diffuse mesothelioma. Environ. Res. 3:330, 1970.

164. Harrington, J. S., J. C. Wagner, and M. Smith: The detection of hyaluronic acid in pleural fluids of cases with diffuse pleural mesotheliomas. Br. J. Exp. Pathol. 44:81, 1963.

165. Thompson, M. E., P. A. Bromberg, and J. S. Amenta: Acid mucopolysaccaride determination. A useful adjunct for the diagnosis of malignant mesothelioma with effusion. Am. J. Clin. Pathol. 52:335, 1969.

166. Castor, C. W., and B. Naylor: Acid mucopolysaccharide composition of serous effusions. Study of 100 patients with neoplastic and non-neoplastic conditions. Cancer 20:462, 1967.

167. Rasmussen, K. N., and V. Farber: Hyaluronic acid in 247 pleural fluids. Scand. J. Respir. Dis. 48:366, 1967.

168. Klempman, S.: The exfoliative cytology of diffuse pleural mesothelioma. Cancer 15:691, 1962.

169. Naylor, B.: The exfoliative cytology of diffuse milignant mesothelioma. J. Pathol. Bacteriol. 96:293, 1963.

170. Roberts, G. H., and G. M. Campbell: Exfoliative cytology of diffuse mesothelioma. J. Clin. Pathol 25:577, 1972.

171. Elmes, P. C., and M. J. C. Simpson: The clinical aspects of methothelioma. Quart. J. Med. 45:427, 1976.

172. Wang, N.: Electron microscopy in the diagnosis of pleural mesotheliomas. Cancer 31:1046, 1973.

173. Kay, S., and S. G. Silverberg: Ultrastructural studies of malignant fibrous mesothelioma of the pleura. Arch. Pathol. 92:449, 1971.

174. Kannerstein, M., J. Churg, and W. T. E. McCaughey: Asbestos and mesothelioma: A review. Pathol. Annu. 13:81, 1978.

175. Kannerstein, M., J. Churg, and D. Magner: Histochemical studies in the diagnosis of mesothelioma. In: Biological Effects of Asbestos, P. Bogovski, et al., eds., Lyon, International Agency for Research Against Cancer, page 62, 1973.

176. Stanton, M. F., and C. Wrench: Mechanisms of mesothelioma induction with asbestos and fibrous glass. J. Natl. Cancer Inst. 48:797, 1972.

177. Stanton, M. F., M. Layard, A. Tegeris, et al.: Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimension. J. Natl. Cancer Inst. 58:587, 1977.

178. Meurman, L. O., R. Kiviluoto, and M. Hakama: Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. Br. J. Ind. Med. 31:105, 1974.

179. McDonald, A. D., and J. C. McDonald: Mesothelioma after crocidolite exposure during gas mask manufacture. Environ. Res. 17:340, 1978.

180. McDonald, A. D., and J. C. McDonald: Malignant mesothelioma in North American. Cancer 46:1650, 1980.

181. Artvinli, M., and Y. I. Baris: Malignant mesotheliomas in a small village in the Anatolian region of Turkey: an epidemiologic study. J. Natl. Cancer Inst. 63:17, 1979.

182. Harington, J. S.: Fiber carcinogenesis: Epidemiologic observations and the Stanton hypothesis. J. Natl. Cancer Inst. 67:977, 1981.

183. Jaurand, M-C, H. Kaplan, J. Thiollet, et al.: Phagocytosis of chrysotile fibers by pleural mesothelial cells in culture. Am. J. Pathol. 94:529, 1979.

184. Rajan, K. T., J. C. Wagner, and P. H. Evans: The response of human pleura in organ culture to asbestos. Nature 238:346, 1972.

185. Chahinian, A. P., and J. F. Holland: Treatment of diffuse malignant mesothelioma: A review. Mt. Sinai J. Med. 45:54, 1978.

186. Anderson, H. A., R. Lilis, S. M. Daum, et al.: Household-contact asbestos neoplastic risk. Ann. N. Y. Acad. Sci. 271:311, 1976.

187. Newhouse, M. L., and H. Thompson: Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. Br. J. Ind. Med. 22: 261, 1965.

188. Selikoff, I. J., W. J. Nicholson, and A. M. Langer: Asbestos air pollution. Arch. Environ. Health 25:1, 1972.

189. Holt, P. F., and D. K. Young: Asbestos fibres in the air of towns. Atmos. Environ. 7:481, 1973.

190. Report of the Advisory Committee on Asbestos Cancers to the Director of the International Agency for Research on Cancer. In: Biological Effects of Asbestos, P. Bogoviski, J. C. Gilson, V. Timbrell, et al., eds., Lyon, IARC Scientific Publications, Number 8, page 341, 1973.

191. Weiss, W: Cigarette smoking and diffuse pulmonary fibrosis. Arch. Environ. Health 14:564, 1967.

192. Jodoin, G., G. W. Gibbs, P. T. Macklem, et al.: Early effects of asbestos exposure on lung function. Am. Rev. Respir. Dis. 104:525, 1971.

193. Rossiter, C. E., and H. Weill: Ethnic differences in lung function: Evidence for proportional differences. Int. J. Epidemiol. 3:55, 1974.

194. Becklake, M. R., G. Fournier-Massey, C. E. Rossiter, et al.: Lung function in chrysotile asbestos mine and mill workers of Quebec. Arch. Environ. Health 24:401, 1972.

195. Bader, M. E., R. A. Bader, A. S. Tierstein, et al.: Pulmonary function and radiographic changes in 598 workers with varying duration of exposure to asbestos. J. Mt. Sinai Hosp. 37:492, 1970.

196. Weill, H., M. M. Ziskind, C. Waggenspack, et al.: Lung function consequences of dust exposure in asbestos cement manufacturing plants. Arch. Environ. Health. 30:88, 1975.