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Review of general disease

Asbestos-related benign disease and cancer: symptoms and treatment

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Long lasting occupational exposure to asbestos dust may cause skin corns, benign pleural effusion, hyaline plaques of the parietal pleura, diffuse thickening of the pulmonary pleura, and asbestosis, i.e. diffuse interstitial pulmonary fibrosis. Malignant disorders include lung cancer and mesothelioma of the pleura, peritoneum and pericardium. In general, many years elapse from first exposure to the appearance of symptoms. Almost all these diseases are the result of dusty working conditions more than 20 years ago. In spite of the fact that the general public is invariably exposed to small amounts of the material, asbestos is not a public health problem. Even living in a building containing sprayed asbestos is calculated to produce a lifetime risk of death which is negligible. There is no evidence to indicate that ingested asbestos fibres represent a major health problem.

Key words: Asbestosis, plaques, lung cancer, mesothelioma, ILO-classification, lung function.

Introduction

Benign asbestos-related diseases include skin corns, benign pleural effusion, hyaline plaques of the parietal pleura, diffuse thickening of the pulmonary pleura, and asbestosis, i.e. diffuse interstitial pulmonary fibrosis.

Malignant disorders caused by asbestos include lung cancer and malignant mesothelioma of the pleura, peritoneum and pericardium.

Millions of workers all over the world have been exposed to asbestos fine dust during the last century. It is therefore not surprising that in some countries lung cancer and mesothelioma caused by asbestos represent the most frequent causes of death of all occupational cancers. Asbestos has been recognized as an occupational health hazard since the beginning of this century. An excellent review of the history of asbestos-related diseases has been written by Browne.[1]

The first description of asbestosis was in 1907. The word 'asbestosis' was coined in 1927. During the first half of the twentieth century the main problem was the distinction between tuberculosis, silicosis and asbestosis. In 1930, the first regulations to control dust emission in certain processes of asbestos manufacture, and to prescribe medical surveillance of employees and compensation for anyone suffering from asbestosis, were instituted in Great Britain.

In the mid-1930s the first case-reports drawing attention to a possible relationship between asbestosis and lung cancer appeared. In Germany asbestosis was accepted as an occupational disease in 1936, and already in 1941 cancer of the lung in association with asbestosis was also accepted as an occupational disease. In other countries acceptance of these relations took many more years.

The clear-cut epidemiological proof for the relationship asbestosis and cancer of the lung was given in 1955 by Sir Richard Doll,[2] who published the first historical cohort mortality study of asbestos workers and found that the lung cancer standardized mortality ratio (SMR) was greatly increased in men with asbestosis, but not in those without.

It is now often forgotten that it was only in 1960 that Wagner published his 33 cases of mesotheliomas, all linked to the exposure to crocidolite in South Africa.[3]

Benign asbestos-related disease

Asbestos warts or corns

These used to appear on the hands and forearms of asbestos workers. There are no reports which would document an association with local mal-

ignancy of the skin. Therapy consists in removal of the spicules of fiber. They are of no major importance.

Benign pleural effusion

Eisenstadt[4] was first to report a case of recurrent and otherwise unexplained bilateral pleural effusion in an asbestos exposed worker in 1965. This syndrome has subsequently been fully accepted as being due to asbestos exposure. Converging linear shadows or rounded atelectasis are a positive radiological diagnostic point. A majority of cases are found to be symptom free. Some may show shortness of breath and pleuritic pain. A blood-stained effusion is found in about one-half of the cases. Sometimes the effusion is eosinophilic. The ESR is often, but not always, raised. The effusion may be bilateral. It appears that this disease is less common with workers exposed to chrysotile only.

These effusions normally absorb spontaneously within a few months. About 30% recurrencies have been observed. A small number have multiple recurrencies. Some will develop widespread diffuse pleural thickening later.

Hyaline plaques of the parietal pleura

Here one is dealing with circumscribed, bilateral raised areas of fibrosis on the inner surface of the ribcage and on the diaphragm. Often, they are partially calcified. Roughly about one-third to one-half of all those occupationally exposed to asbestos containing amphiboles and followed up for a minimum of at least 30 years will be found to have calcified plaques. The incidence in various studies is different, because of factors such as type of fiber involved, consideration of calcified and/or non-calcified plaques, methodology of X-ray technique, autopsy evaluation or radiographic evidence only, and occupational or environmental exposure must be taken into account. It is important to note that bilateral plaques and asbestosis, i.e. intrapulmonary interstitial fibrosis, do not necessarily occur together. The lesions are usually a few millimeters to one centimeter thick. They are of irregular shape with a smooth, polished, slightly convex ivory-colored surface, resembling articular cartilage. Some are multinodular, and others consist of a combination of both forms. The plaques consist of avascular, acellular, laminated collagen fibers. Some fibroblasts may be found between the fibers. Asbestos fibers and asbestos bodies have been found in both normal parietal pleural tissue and plaques. Interestingly enough, some recent studies suggest that pleural calcification is related to tremolite or some other contaminant of chrysotile ore, present in some mines. Another amphibole that might be of importance is anthophyllite.[5] Browne[5] suggests that the rare insoluble amphibole fiber, too long to be transported onwards by macrophages, lodges in the pleural region and causes, through the stimulus of mediators produced either by macrophages or by the mesothelial cells themselves, the characteristic plaque reaction. The final pathomechanism is, however, unknown.

Pleural plaques alone, whether calcified or not, are symptomless and do not hinder the normal respiratory excursion. Lung function is normal in the absence of accompanying radiographic evidence of diffuse intrapulmonary fibrosis. Plaques themselves have no effect on life expectancy. They are not known to give rise to any complications.

Diffuse pleural thickening

Again, it is extremely difficult to assess the true incidence of this disease entity, as many factors come into play as described under pleural plaques. Hillerdal finds a relation of diffuse pleural thickening to pleural plaques of 1:6.[6] Initially, a thin layer of fibrosis over the lower half of the lungs produces a slightly diffuse loss of translucency. Only later, and where there has been resolution of an effusion, is fibrosis more widespread, with fusion of the visceral and parietal pleural layers.

In contrast to hyaline plaques of the parietal pleura, diffuse thickening has been shown to have an adverse effect on lung function. Again, it is difficult to separate the effect due to the diffuse thickening from the underlying early or radiographically undetectable asbestosis. Diffuse thickening, of course, is obscuring the parenchyma in the radiograph. Bilateral diffuse pleural thickening increases the sedimentation rate. About 20% of these patients experience pain.

In men heavily exposed to asbestos and followed up for more than 15 years, about 20% will be found to develop diffuse pleural thickening with or without accompanying parenchymal abnormality. Most will have occurred early in the observation period, and the incidence is much higher in subjects with progressing asbestosis. There is no evidence that diffuse pleural thickening is likely to predispose to malignancy.

In diffuse pleural thickening the costophrenic angle is almost always obliterated. It should be observed that pleural plaques normally do not involve apices or costophrenic angles. The onset may be unilateral, but later diffuse pleural thickening is usually bilateral but asymmetrical. It is important to distinguish it from subpleural fat pads. When doubt arises on a PA film the diagnosis can usually be made by oblique films. Sometimes computer tomography is required.

Asbestosis

Here too there are few accurate statistics regarding the true incidence of the disease. Actually one cannot expect such statistics since the dust concentrations in the workplace have changed continuously over the years and simultaneously the diagnostic criteria for establishing asbestosis have also changed. The result of this fact is that today cases with early signs of disease are earlier accepted than they would have been decades ago. This could simulate a shorter exposure time, whereas of course the opposite is true.

An important term which is often used in this connection is *cumulative exposure*. It is expressed in f/cm^3 years (where f = fibers), i.e. it represents the product of the average dust level in f/cm^3 to which the subject is exposed and the number of years worked at this average level.

It has not yet been settled, whether the dose–response relationship is linear and whether a threshold exists below which no effect is experienced. The Ontario Royal Commission concluded in 1984 that a linear relationship was consistent with published studies.[7] The Commission also concluded that a threshold exists so that asbestosis will not progress to clinical manifestation at or below lifetime occupational exposure of 25 f/cm^3 years.

In histology the earliest stage identifiable in man is a plastering of the alveoli from within the lumen of the respiratory bronchioles. Patchy bronchiolitis obliterans may develop. Later fibrosis spreads peripherally into the alveolar ducts and alveolar walls, obliterating many alveoli especially in the subpleural regions. It is now called diffuse interstitial pulmonary fibrosis (DIPF). It is important to realize that fibrosis may be found when its presence is not suspected on gross examination. Quite clearly early pathological changes precede clinical, physiological and radiographic evidence of the disease. It is therefore important for the pathologist to sample various areas and to include central and peripheral portions of all lobes.

Microscopically numerous *asbestos bodies* (ferruginous bodies) can usually be seen. Asbestos bodies are formed around asbestos fibers, usually long fibers, i.e. more than 10 μm long, which are enclosed within a chain of macrophages forming a giant cell. The capsule of the asbestos body contains ferritine. Asbestos bodies can persist unchanged for years but segmentation takes place over the years in an increasing proportion. Not all asbestos bodies contain asbestos fibers in their center; their cores may consist of carbon, graphite, mica, talc or various clays or of the siliceous bodies of diatoms. When the central core is asbestos, it is found to be preponderantly amphibole in environmentally exposed humans. It is now generally accepted that, if searched for with sufficient diligence, asbestos bodies can be found in the lungs of all adults living in cities. Asbestos bodies may also be found in the spleen, thyroid and pancreas. Various attempts have been made to correlate the number of asbestos bodies and the severity of interstitial lung disease by counting bodies in histological slides in sputum or in bronchoalveolar lavage fluid. It is accepted that the concentration of asbestos fibers, but not necessarily asbestos bodies, increases in proportion to the degree of pulmonary fibrosis up to asbestosis of moderate degree, but there is no such correlation in advanced cases.

Unfortunately there is no universally agreed system of assessing the degree of asbestosis histologically. Often the scheme given by Craighead *et al.* is used.[8]

- *Grade 0.* No fibrosis is associated with bronchioles.
- *Grade 1.* Fibrosis involves the wall of at least one respiratory bronchiole with or without extension into the septa of the immediately adjacent layer of alveoli; there must still be a zone of non-fibrotic alveolar septa between adjacent bronchioles.
- *Grade 2.* Fibrosis appears as in grade 1, plus involvement of alveolar ducts or two or more layers of adjacent alveoli; there must still be a zone of non-fibrotic alveolar septa between adjacent bronchioles.
- *Grade 3.* Fibrosis appears as in grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchioles have thickened, fibrotic septa; some alveoli may be obliterated completely.
- *Grade 4.* Fibrosis appears as in grade 3, but

with formation of new spaces of a size larger than alveoli, ranging up to as much as 1 cm; this lesion has been termed honeycombing. Spaces may or may not be lined by epithelium.

Unfortunately also there is no standardized method for measuring the quantity of asbestos fibers in biological material in an accurate and reproducible manner. Interlaboratory variations are considerable. Great caution is necessary in the interpretation of such figures. Optical microscopy cannot discriminate between asbestos and many other fibers. Even by phase-contrast microscopy only about 5–15% of fibers visible by transmission electron microscopy (TEM) can be seen. A more accurate analysis can only be obtained with TEM equipped for energy-dispersive X-ray analysis (EDAX) which can detect and identify almost all fibers. This equipment is very expensive, requires considerable expertise and is very time-consuming.

The importance of fiber length. By now there is little doubt that long fibers produce a much greater fibrogenic effect than short fibers. There is now good experimental evidence that animals given the same type of fiber but containing a substantial proportion longer than 5 μm develop interstitial fibrosis, whereas short fibers produce no more reaction than controls. There is also excellent clinical confirmation of this finding. In a case–control study using TEM Sébastien *et al.*[9] showed that only long amphibole fibers, i.e. longer than 8 μm, were associated with excess mesothelioma and thus massive exposition (see below). Counts of fibers shorter than 8 μm did not contribute to the discrimination.

The major difference between the amphibole and chrysotile fibers is the degree to which the fiber is insoluble in pulmonary tissue. Especially considering animal experimental studies, it is of the utmost importance to consider the durability of fibers in the tissues in relation to the life span of these animals.[10] An extensive and excellent discussion of all the problems regarding lung fiber burdens and the attribution of disease, asbestos bodies, the disappearing chrysotile (or chrysotile paradoxon, as it is sometimes called) and persisting amphibole fibers, can be found in Ref. 1.

Clinical diagnosis. Usually the diagnosis is made without any histological examination of lung tissue. Only in rare instances is open lung biopsy indicated when workers are assessed for compensation purposes.

In advanced forms asbestosis is a restrictive lung disease associated with dyspnea, clubbing of the fingers and cyanosis, basilar crackles and widespread irregular opacifications on X-ray photographs. These are more prominent at the lung basis. Usually the hilar lymph nodes are only slightly enlarged and soft unless other disease coexists. Emphysema is unusual. Diffuse pleural thickening and/or pleural plaques as discussed above may also be present. The vital capacity is usually reduced with preservation of the FEV1/FVC ratio and gas exchange impaired. Cor pulmonale may occur in advanced disease. Chest roentgenography appears to be the most valuable examination in diagnosing asbestosis.

Chest X-ray and ILO classification. A diffuse irregular interstitial pattern coupled with evidence of pleural disease, e.g. plaques or extensive pleural thickening in a person with known exposure, presents little diagnostic difficulty. The difficulties occur with the radiological detection of lesser degree interstitial fibrosis. Efforts have been made to standardize the interpretation of roentgenograms in the pneumoconioses. The most widely accepted and extensively studied method for assessing the degree of roentgenological involvement in pneumoconioses was developed by the International Labour Office (ILO) and is currently called the ILO-1980 Classification.[11] This scheme evolved from studies of miners and focused initially on the detection of silicosis. The X-ray appearance of silicosis is characterized initially by small rounded opacifications. The classification was later broadened to describe abnormalities which occur in asbestosis and do not have a rounded appearance. These are fine, medium and coarse, small irregular opacifications, and they are called s, t, and u, respectively. The classification, originally developed for describing radiological changes in epidemiologic studies, has also been used in the clinical context for case detection and/or diagnosis. In the latter instance, the information given in the chest radiograph is added to all other information about the individual in order to arrive at a diagnosis.

The number of these abnormalities in a given area of the chest film, whether rounded or irregular, is called their *profusion*. The profusion was initially graded as 0 for none, 1 for slight, 2 for moderate, and 3 for severe. It became apparent, however, that even experienced readers had difficulty in grading opacifications into these categories in a reproducible fashion. However, if observers were asked to give two classifications, i.e. the one category they

thought was most likely and another which they thought might also be considered, the observer reliability (in terms of reproducibility) was considerably improved. This method of giving the observer two options was called the expanded classification. It formed a 12-point scale that has proven to be very useful epidemiologically. It is likely that an individual who develops asbestosis moves more or less uniformly from normal roentgenological appearances (–/0, 0/0, 0/1) to the abnormal (1/2, 2/1, 2/2, etc.). The problem is that the interpretation of the lesser degrees of abnormality on this scale is subjective and that numerous causes other than asbestosis may produce the described radiological changes. In the presence of marked diffuse pleural thickening, it is difficult to diagnose or grade the severity of interstitial fibrosis. Accordingly, criteria other than the roentgenographic have been sought.[12]

During the Seventh International Pneumoconioses Conference in Pittsburgh[13] these problems were extensively discussed. A large number of papers criticizing the ILO classification and making new propositions regarding its improvement were presented. It was decided to institute a committee preparing yet another modification of the ILO classification. Most of the alterations will concern the interpretation of pleural changes. Also, it became clear that there is an initial tendency to overread X-rays by physicians volunteering to participate in a Canadian scheme. Even certified, advanced, so-called 'B' readers in the USA found more abnormalities than the most expert readers, namely those instructing the course leading to NIOSH certification. The overwhelming causes of false positive diagnosis of small opacities are lack of radiographic sharpness, blurring from respiratory movement and poor exposure.

Lung function. Typical signs are those of restrictive lung disease, i.e. reduction in lung volume with inspiratory capacity and vital capacity being primarily affected, functional residual capacity being less affected and residual volume even less.

These changes are consistent with a decrease in pulmonary compliance. Large airway function as reflected in the FEV1/FVC ratio is generally well preserved. Review of the prediction formulas for pulmonary function tests reveals there is no one set applicable to all laboratories and patient populations. Predicted normal values used in pulmonary function laboratories should be based on regression equations from studies whose testing equipment, methodologies and control populations most clearly resemble the patients under study. Numerous studies have shown that the effects of asbestos on lung function are dose related. There is convincing evidence that an asbestos-related pulmonary abnormality can occur in the absence of definite radiological change. These pathological changes of early asbestosis have been demonstrated in biopsy material from asbestos-exposed individuals with minimal or no radiological abnormality. Similarly, exposure–response relationships for certain pulmonary function abnormalities have been demonstrated in asbestos-exposed subjects without radiological abnormalities or reduction in vital capacity. The impairment associated with such abnormality is usually modest. Hypoxemia may be present at rest or develop with exercise. Diffusing capacity is also usually impaired, depending on the extent of the disease.

A reduction of the diffusing capacity in an asbestos worker in the absence of other known causes for impairing gas exchange does provide suggestive evidence for asbestosis.

This section on lung function, as outlined by the American Thoracic Society and adopted by the ATS Board of Directors, March 1986, is still valid.[12]

Dyspnea. There is no doubt that shortness of breath is common and troublesome in individuals with clinically significant interstitial fibrosis. Dyspnea, however, is a non-specific symptom, common in many other cardiopulmonary disorders, and it is particularly subject to emotional factors likely to be relevant in instances of suspected occupational disease. Accordingly, it is not adequate to use dyspnea as the only evidence on which to base a clinical diagnosis of asbestosis in an individual at risk.

Clubbing. Clubbing of the fingers occurs more commonly in asbestos-exposed workers than in controls. The diagnostic usefulness of clubbing is limited, however, by two important considerations. There are many other causes of clubbing and clubbing, when present, is a late finding in pulmonary asbestosis. Since the majority of persons with significant asbestosis do not have clubbing, and asbestos workers with clubbing may have it for reasons other than pulmonary fibrosis, the diagnostic usefulness of clubbing is limited.

Basilar crackles. Characteristically the crackles of interstitial fibrosis are pan-inspiratory or have an end-inspiratory accentuation. They appear first at the bases in the mid-axillary lines and tend to spread

towards the posterior bases. As the disease advances, the crackles progress up to higher levels. About half of the persons considered to have asbestosis on clinical grounds have crackles. Crackles unfortunately are not specific for interstitial fibrosis related to asbestos, but may be useful in diagnosing the disease.

Gallium scanning, bronchoalveolar lavage, transbronchial biopsy. All these new diagnostic techniques need further evaluation with respect to their usefulness in diagnosing asbestosis.

Comment. The above-mentioned diagnostic criteria for non-malignant asbestos-related diseases as published by the American Thoracic Society[12] have been challenged by Franzblau and Lilis.[14] Quite rightly they point to the fact that, even though asbestos consumption in the Western countries has decreased drastically during the last decade, total world consumption, and especially the consumption in Third World countries, has actually increased, and is still increasing. However, this of course does not necessarily mean that the incidence of asbestos-related diseases is also going to increase, since there is good evidence that, even in Third World countries, appropriate measures for proper dust control have been taken. The rest of Franzblau and Lilis's discussion is political rather than medical. One can only agree with Murphy and co-workers'[15] answer in which they repeat that asbestosis is a pnemoconiosis, consequent to asbestos exposure, using the term pneumoconiosis as defined by the World Health Organization as: "the accumulation of dust in the lungs and the tissue reaction to its presence". The term 'pleural asbestosis'[16,17] definitely should not be used and only confuses patients and doctors and leads to mistaken prognostic information. It is important to realize that the American Thoracic Society's use of the term asbestosis is in line with that used by the government of Canada, Great Britain, the American College of Radiology, the American College of Chest Physicians, the American College of Pathology and many other official organizations.

Obviously Drs Franzblau and Lilis are concerned with matters of workers' compensation and third-party liability. Franzblau and Lilis prefer the 'cookbook' approach of diagnosing asbestosis. This may not be done. Specifically, these authors would like to state that any chest X-ray labeled as 1/0 would represent asbestosis. However, by definition, this implies that 0 or normal is a serious consideration. That means that, in the circumstances of attempting to diagnose early interstitial fibrosis, which has been called the most subjective area in chest roentgenology, the reader is stating that he, himself, seriously considers normal as alternative reading. Some readers interpret 1/0 as a point on the 12-point scale, i.e. they mean that the graduation is more than 0/1 but less than 1/1, rather than that they have considered 0 as an alternative classification. Taken in this light, some readers mean that they are diagnosing early asbestosis when they use the term 1/0. Thus a term that has two different meanings is confusing at best.[15]

Since there is yet no standard X-ray for 1/0, ILO will provide more standard films in the future, when a new classification is going to be introduced.

Also, it is important to realize that the classical picture of asbestosis is often modified by the presence of chronic obstructive pulmonary disease due to smoking.

Immunological considerations

As with so many other diseases, differences in susceptibility to asbestos-related diseases among workers employed on similar tasks quite clearly exist. A large number of well-controlled immunological studies comprising various techniques have therefore been carried out. However, as summarized by Browne,[1] all the positive results so far found have been inconstant, unpredictable and uninterpretable in the clinical context. They are probably epiphenomena unrelated to the disease causation, and individual differences in response may relate better to lung structure or lung function than to immunological factors. Therefore all hopes existing since the early days of a pre-employment test for asbestos workers, which would identify the susceptibles, still remain dreams.

Prognosis and therapy

Before and during World War II asbestosis was an occupational disease of great importance. Now the incidence has declined drastically owing to impressive improvement in dust elimination. Actually asbestosis is a disappearing disease and prospective studies are no longer possible, and it is almost impossible to demonstrate to a medical student patients with clear-cut asbestosis. Outside the working environment asbestosis has not been observed. In the newly diagnosed cases the disease is relatively mild and probably will not progress.[18]

Unfortunately there is no effective therapy for established disease.

Asbestos-related malignancy

Only the most important clinical facts are given below. Various reviews have been written recently,[19–26] and some excellent books dealing with mesothelioma and asbestos-related lung cancer have appeared.[27,28]

The evidence that asbestos-caused lung cancer is related to asbestosis is overwhelming. Seen on a world-wide basis, this form of cancer is probably more important from a quantitative point of view.

Asbestos-related lung cancer

There is no doubt that exposure to all forms of asbestos and cancer of the lung are associated. This is documented in a large number of well-controlled epidemiological studies.[28] The average latency period of the disease from the onset of exposure to diagnosis is around 20 years. It has long been recognized that smoking habits are of the utmost importance since lung cancers among asbestos workers who do not smoke are extremely rare. The problem of whether asbestos and smoking combine in a multiplicative fashion or in an additive way only has not been solved. Also, it might never be solved since there are so many coexisting additional important factors such as type of asbestos fibers inhaled, surface characteristics of these fibers, concentration, exposure time and other carcinogenic substances used in the workplace. There is usually a dose–response relation between cancer incidence and total amount of asbestos fine dust inhaled, as expressed in cumulative fiber years. Textile workers dealing with amphiboles show a higher relative risk of disease than others. Low incidences are found in workers of plants where friction products are manufactured and in chrysotile miners.

The extensive debate regarding the importance of passive smoking might also be extremely important in this context. Since many asbestos workers used to be heavy smokers, this factor could be pertinent for the non-smokers. At the moment it is impossible to say on epidemiological grounds whether there is any difference between the various asbestos fibers in causing lung cancer in non-smokers.[28] Large cohorts would be needed in order to assess such a problem, and such cohorts simply do not exist, since most asbestos workers have been smokers.

There is no evidence for the belief that environmental asbestos fiber concentrations have ever caused lung cancer in the general population. This actually is not to be expected, considering that fiber concentrations are at levels several hundred or thousand times lower in the environment than those found in workplace situations in the past.[20]

That scar cancers in patients with tuberculosis do exist is not doubted by anybody. Doubtless also interstitial pulmonary fibrosis not due to asbestos is sometimes associated with tumorigenicity.

Warnock and Isenberg[31] question the view that most asbestos workers with lung cancer have histopathological evidence of asbestosis on in-depth examination. To a large extent this must be a methodological problem, depending very much on the care used by the pathologist carrying out the examination and depending on the number of sections made.[29,30]

I would only like to stress two points:

(1) in asbestos tumors there is a reversal of the usual upper to lower lobe ratio;
(2) there is an increase in the proportion of adenocarcinomas to other types.[1]

Diagnosis, therapy and prognosis do not differ from lung cancer not caused by asbestos fibers.

Mesothelioma

In contrast to the situation in bronchogenic carcinoma, smoking has no influence on the prevalence of malignant mesothelioma in humans.[28] As compared with the mortality due to lung cancer, which is approximately 130 000 cases/year in the United States, an average of 1500 cases of malignant mesotheliomas are reported yearly.[32]

One of the most interesting facts is that the mortality due to mesothelioma in women of all ages and in men under 65 years in age has remained fairly constant or declined slightly. However, death rates in men aged 65 or older have increased steadily. This means that there have always been mesotheliomas unrelated to asbestos exposure. It is estimated that about 80% of all diffuse malignant mesotheliomas occur in men exposed to asbestos in the workplace. In the remaining 20% with malignant mesothelioma, there is neither history of exposure to asbestos nor excess of mineral fibers in their lungs.[28]

If not stated otherwise we are talking in the

following about pleural mesotheliomas, but there are of course peritoneal and pericardial mesotheliomas as well (see below).

It should be observed that asbestos does not cause localized benign, predominantly fibrous, mesothelioma.

Clinical appearance. Patients with malignant pleural mesothelioma may be asymptomatic at first, but they often have dyspnea or chest pain with pleural fluid of variable mobility.[28] Pleural thickening or interstitial fibrosis is apparent on chest films in approximately 20% of the patients and computerized tomography scans reveal calcifications of the tumor mass in almost half of the patients. Since malignant mesotheliomas vary histologically, ranging from epithelial to sarcomatous and mixed forms, diagnosis by microscope is difficult. The tumors may be confused with those of metastatic cancer or, less commonly, with inflammatory or reactive processes, including exuberant mesothelial hyperplasia. When the tumor appears in a glandular or tubulopapillary pattern, it may be misdiagnosed as a metastatic adenocarcinoma.[20]

Diagnosis. Advances in histochemistry, immunocytochemistry, and electron microscopy have made possible earlier and more accurate diagnosis of malignant mesothelioma, if sufficient biopsy material is available. Generally, cytological smears or needle-biopsy specimens do not allow an accurate identification, and only open thoracotomy yields tissue samples adequate for both the diagnosis of malignant mesothelioma and the determination of fiber counts in the lung.[28] New diagnostic possibilities are opened by electron microscopy, where the unique fine features of mesothelioma cells such as long microvilli and tonofilaments can be seen.[28]

Prognosis. The prognosis of malignant mesothelioma is still bad. Most patients survive for less than one year after diagnosis, although untreated persons have survived for as long as three years. A combination of radiation and doxorubicin (adriamycin) is probably most helpful in prolonging survival,[28] and thoracocentesis can minimize dyspnea.[20]

Latency period. The average latency period between the first exposure to asbestos and the clinical diagnosis of malignant mesothelioma is 30 ± 10 years, with most deaths occurring in patients over 60 years of age.[27]

Is there evidence for a threshold for asbestos-related mesotheliomas? Ilgren and Browne[33] have reviewed the relevant literature dealing with results from studies of animals and patients supporting the concept of a mesothelioma threshold. They feel that such a threshold is very likely in view of the existence of a distinct background incidence of spontaneously occurring and non-asbestos-related mesotheliomas,[34] the high occupational dosis associated with the appearance of mesotheliomas in humans, and the large number of 'tumorigenic' fibers required to produce significant numbers of mesotheliomas in animals. They show very nicely that even when the duration of exposure associated with the appearance of mesotheliomas in humans has been brief, the exposure itself has been intense.

The influence of fiber type. The major difference between chrysotile and the amphiboles has been confirmed beyond reasonable doubt in epidemiological and experimental studies.[35] An outstanding discussion of the problem can be found in Ref. 1.

Peritoneal mesothelioma. The ratio of pleural to peritoneal sites is about 10:1 in males and 5:1 in females.[1] Misdiagnosis of peritoneal cases is frequent. In occupationally related mesotheliomas pleural localization predominates, whereas in background cases it is probable that the ratio approximates 2:1.

The onset of symptoms may be insidious. First there is poorly localized abdominal discomfort with loss of appetite and weight and, in some instances, constipation. Painless, diffuse swelling of the abdomen with increasing abdominal girth may be the first symptom. In about one-third of cases symptoms of intermittent upper or lower intestinal obstruction occur, which may or may not be associated with colicky pain.[1]

Physical signs. Abnormal signs are often absent on initial examination but soon some diffuse abdominal fullness is evident and the signs of ascites may be present.[36] Later the abdomen is much distended and its girth may increase rapidly. At this stage firm masses are usually palpable by direct or bimanual palpation, although it is not possible to relate these to any abdominal organ. The patient is now ill and emaciated.

Radiological changes. Signs of bilateral calcified pleural plaques or asbestosis may be present in the chest film. Occasionally there is evidence of

invasion of the pleura on one or both sides in advanced disease. Otherwise the occupational history is decisive. If there is a history of asbestos exposure, radiography of the abdomen, evidence of small or large bowel obstruction, with or without ascites, displacement of intra-abdominal structures by soft tissue masses, or diffuse extrinsic indentation of the bowel with submocusal infiltration and encapsulation shown by barium meal or enema suggests the possibility of a mesothelioma. As with pleural disease, computerized tomography may sometimes be helpful.[11]

Pericardial mesotheliomas. Pericardial mesotheliomas can be primary or metastatic from the pleura and perhaps the peritoneum. As Spodick shows,[37] his seven patient presented as having either 'typical' acute pericarditis or, more commonly, cardiac tamponade; two patients suffered constrictive pericarditis.

Other malignant diseases?

Gastrointestinal cancer. Some authors believe that asbestos exposure is associated with an excess risk of gastrointestinal cancers.[38] They refer to a so-called 'meta-analysis' by Frumkin.[39] However, these authors have selected cohorts as a proxy for exposure to asbestos. They acknowledge that the misdiagnosis of mesotheliomas or lung cancers invalidates the use of lung cancer SMR as a meaningful proxy of exposure, and cast doubt on the conclusions. That misdiagnosis is of such great importance in this field has been beautifully described by Doll and Peto.[23] A further reassessment of the problem is given by Edelman.[41] He analyzed the results of published studies on 32 independent cohorts. His conclusions were as follows: "No consistent evidence was found to indicate that exposure to asbestos increases the risk of gastrointestinal cancer. Generally, the higher SMRs came from studies conducted in the United States or Canada and might reflect factors not related to exposure to asbestos. In studies in which asbestos exposed and non-asbestos exposed workers were evaluated, the SMRs were not consistently higher for the group exposed to asbestos. There was no apparent dose response relation between accumulated asbestos dose and the risk of gastrointestinal cancer. It is concluded that there is no dose–response relation between exposure to asbestos and risk of gastrointestinal cancer, and asbestos workers are not at an increased risk of gastrointestinal cancer."

Asbestos in drinking water. The problem of an increased ratio of gastrointestinal cancers has been brought into correlation with asbestos fibers in drinking water. Despite the demonstration that a small number of ingested fibers can be recovered from the gastrointestinal lymph, animal experiments have consistently failed to show any effect of ingested asbestos on gastrointestinal malignancies. A large number of epidemiological studies has been reviewed by MacRae.[42] The conclusion is that the data provide no evidence of a specific relationship between ingested asbestos and gastrointestinal malignancy.

Asbestos fibers in urine. A recent study shows that workers exposed to chrysotile fine dust excrete chrysotile fibers in urine, but there was no statistically significant difference as compared with control workers not being exposed to chrysotile.[43]

Laryngeal cancer. The main difficulty in assessing an asbestos effect on the incidence of laryngeal cancer arises because of the major confounding effects of alcohol, tobacco and social class. Moreover, dusty trades and the construction and lagging industries have always tended to have a higher labour turnover, with a greater proportion of single men with an atypical lifestyle resulting in higher SMRs for violence, suicide and lung cancer and higher tobacco and alcohol consumption. Few studies of laryngeal cancer in asbestos workers have been controlled adequately for these confounding factors. Recent reviews by Chan and Gee[44] and Edelman[45] show that, when such studies are examined critically, there is no support for a specific causal relationship with asbestos exposure.[1]

Lymphoproliferative disorders. We would agree with Browne's summary,[1] that the epidemiological evidence is against a direct relationship between asbestos exposure and the development of either lymphoma or leukemia.

Concluding remarks

Asbestos-related diseases belong to the group of best-investigated and documented disease entities.[40] Already up to 1986 about 10 000 references plus abstracts have been compiled from the world literature by Pelnar in his three-volume compendium,[46–48] and the flow of new papers has not ceased since. To the non-specialist in this field it is therefore perhaps surprising that new knowledge is

still being added. The new information stems from various sources since this field is truly interdisciplinary. As I have tried to show in this paper, several issues are still unsolved, unclear or even controversial. However, evidence is accumulating that occupationally caused mesotheliomas, i.e. non-background mesotheliomas, are mainly, if not exclusively, due to amphiboles and not to chrysotile.[49,50] It is therefore most important always to distinguish between the various types of asbestos when discussing associated diseases. 'Asbestos' is not just 'asbestos'. The reason that the amphiboles as compared with chrysotile, which belongs to the serpentine group, show an increased pathogenicity is probably the insolubility of the amphiboles in both animal and human tissues and/or a different pattern of deposition and clearance from the lung.

Another reason why asbestos research is still so interesting is the fact that asbestos fibers have provided a model of carcinogenesis that may be valuable in discussing the factors leading to neoplastic transformation. Thus new insight into the etiology, pathogenesis and biology of cancer in general may be gained.

Fortunately progress has been made in diagnosing these diseases earlier and evaluating them better, even though therapy remains symptomatic in many instances. Dramatic responses to doxorubicin, particularly in patients with peritoneal mesotheliomas, have been reported.

Progress was also made in evaluating better the influence of asbestos on the general population. The content of asbestos fibers in the air of buildings containing sprayed asbestos is in most instances harmlessly small and essentially the same as in outdoor air.[51] Available data do not support the concept that low-level exposure to asbestos is a health hazard in buildings and schools.[21]

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