PLAINTIFF'S EXHIBIT

UC-2584

Asbestos Criteria
DRAFT 6/4/84
R.L.H. Murphy, M.D.

OBJECTIVE:

The health effects of asbestos have become a cause of serious concern in recent years. It has been estimated that from 1940 to 1979 in the United States alone, 27,500,000 individuals were exposed to this mineral at work. Recognition of the diseases ~~caused by~~ associated with asbestos exposure has led manufacturers to introduce engineering controls, provide personal protective devices and clothing and reduce exposure by using alternative materials and by instituting improved work practices. It has also led to widespread public concern over the presence of asbestos in the environment and fear on the part of persons with a potential for minimal exposure. This and projections of future asbestos related illness have led to important public policy questions; whether to remove all asbestos in public buildings and what to do about the enormous estimated legal liability. In this context physicians are commonly asked for advice on the health effects of asbestos. While abundant literature exists on the health effects of asbestos there is much that is conflicting. Accordingly, this report ~~was~~ has been prepared by a group of experts to present an authoritative concensus view of the current state of knowledge while pointing out areas where additional information is

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 1 of 34 asbestosclaims.law/library/17543/1

necessary. An attempt is made to summarize the extent of the hazard while providing the sources on which the opinion is based.

ASBESTOS - THE MINERAL:

The generic term "asbestos" is used to describe a group of minerals which when crushed break into fibers rather than dust. They are hydrated fibrous ~~hydrous~~ silicates which have great tensile strength, heat resistance, acid resistance and ~~are~~ in some varieties are also flexible. This weavable rock has numerous important uses in an industrial society, and world production and use has climbed steadily since its commercial introduction in the late 19th century. Geology, minerology, and uses have been well described elsewhere (1-3). The common fiber types include chrysotile, amosite (cummingtonite), croccidolite, and anthophylite.

ASBESTOS IN LUNG TISSUE:

Inhaled asbestos that is retained in the lung can become coated with a proteinaceous, Fe staining material. The resulting asbestos or ferruginous body is a most characteristic index of asbestos exposure. It is usually recognized by its beaded-necklace or drumstick appearance. The longer fibers are more likely to become coated (2-22). The majority of the lung burden of asbestos, however, is uncoated and consists of short

A02184

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 2 of 34 asbestosclaims.law/library/17543/2

fibers, i.e., less than 5 µm (2-21). These are poorly visible or invisible on light microscopy but have been demonstrated by electron microscopy. Asbestos bodies are commonly found in routine autopsies in the absence of asbestos related illness. These are usually few in number and point to the importance of developing a standardized technique to quantify the amount of asbestos in lung tissue (to be discussed below).

BENIGN PLEURAL ABNORMALITIES ASSOCIATED WITH ASBESTOS:

Asbestos causes pleural plaques, pleural thickening and pleural effusion. Pleural plaques are discrete, shiny, rounded lesions. They characteristically occur on the posterolateral aspect of the lower parietal pleura, but usually not on the visceral pleura, at the costophrenic angles, or at the apices. Thin plaques are smooth and greyish-white. Thicker ones are ivory colored and may have either a smooth surface or be coarsely nodular with the consistency of cartiledge. Diaphragmatic plaques are usually round and disk-like whereas those over the intercostal spaces are elongated and have an irregular configuration. Microscopically, plaques are seen to be collagenous connective tissue, cell-poor, with few fibrocytic nuclei, arranged in undulating fashion in a coarse,

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 3 of 34 asbestosclaims.law/library/17543/3

basket-weave pattern, and containing only few thin-walled capillaries (23, 24). Elastic staining shows intact lamellae beneath the plaque in continuity with the surrounding normal parietal pleural connective tissue, suggesting that plaques are extrapleural and develop between the latter and its covering layer of mesothelial cells (23). Some calcium deposition is present in a high proportion of plaques, and occurs as granules along the course of the collagen fibers, ceasing abruptly where the connective tissue changes into normal pleural tissue (23). Cuboidal mesothelial cells may occur at the edge of the plaque (23), occasionally with metaplastic changes (24, 25).

Although coated asbestos fibers have not been reported in relation to pleural plaques, in the extensive series of 172 sections examined by Meurman (23) under polarized light, examination of ashed tissue has revealed the presence of uncoated fibers in many cases (26, 27). With electron microscopy, it is apparent that most plaques contain many small, submicroscopic fibers. It is of interest that these are more concentrated in the calcified zones than in the fibrous zones (28).

The usual effect of asbestos on the visceral pleura ~~of asbestos~~ is a focal or diffuse thickening. This varies from a thin milky

A02186

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 4 of 34 asbestosclaims.law/library/17543/4

white discoloration, detectable only on gross visualization, to a thick peel encasing the lung and easily seen on chest roentgenogram. In contrast to plaques, which are most likely a roentgenologic diagnosis in an otherwise healthy person, pleural fibrosis may cause symptoms and impair pulmonary function.

PLEURAL EFFUSION

Asbestos exposure has been associated with development of pleural effusion, usually an exudate that may persist for several months to a year. It may recur on the same or the opposite side after several years. Macroscopically the fluid is often blood stained and microscopically erythrocytes and/or mature lymphocytes are commonly seen (Hillerdal, Gunner Thorax 1981: 36: 669-675).

PULMONARY ASBESTOSIS

DEFINITION

The term asbestosis should be reserved for the interstitial fibrosis of the pulmonary parenchyma due to asbestos. While pleural abnormalities are commonly associated with parenchymal disease, they should be separately classified as there are differences between pleural and parenchymal

A02187

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 5 of 34 asbestosclaims.law/library/17543/5

fibrosis in epidemiology, clinical features and prognosis.

Pathologic Features

In lungs with minimal or moderate fibrosis there may be no changes visible grossly. When they occur, the microscopic changes in pulmonary asbestosis vary from small areas of basal fibrosis to a diffuse, fine fibrosis of both lungs. In general, the more severe the process the smaller the size of the lungs. The cut surface of the lung has a dark brown color with streaks of a fine, grey colored fibrosis that generally appears to affect subpleural areas first, often quite extensively. This fibrosis outlines lobar and lobular septa and focally interdigitates the lung parenchyma. The parenchymal fibrosis, which has a linear and reticular appearance, affects the lower lobes first, then middle lobes, and eventually upper lobes (10, 29, 30). In advanced cases honeycombing is found commonly in the lower lobes and subpleural regions (30). The honeycombing is characterized by cavities that range from 1 to 15 mm and have thick walls (31). The pleural surface adjacent to the fibrosis is invariably involved in the fibrotic process, either mildly, giving the appearance of a milky covering to the fibrosis or with widespread fibrosis and symphysis (29, 30). The hilar lymph

A02138

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 6 of 34 asbestosclaims.law/library/17543/6

nodes are not usually enlarged or otherwise affected (10, 32). There is no evidence that asbestos causes emphysema, but there has been no systematic autopsy study to quantify the degree of emphysema in asbestos workers compared to controls.

Asbestosis is a restrictive lung disease associated with dyspnea, clubbing of the fingers, basilar crackles, and widespread irregular opacifications on roentgenograms. The latter are usually more prominent at the lung bases. Pleural thickening and calcification may also be present as noted above. The vital capacity is usually reduced and gas exchange impaired. Cor Pulmonale is a common result in severe cases of pulmonary fibrosis. When many or all these features are present the diagnosis is made without difficulty. However, in the absence of the opportunity to examine lung tissue microscopically, the diagnosis is always inferential. The certainty increases with increasing numbers and severity of typical clinical abnormalities. We will now review individual features commonly associated with the interstitial lung disease due to asbestos.

When asbestosis is advanced, the chest roentgenogram appears to be the most valuable single examination. A diffuse irregular interstitial pattern coupled with numerous pleural plaques or extensive pleural thickening in a person with known

The availability of a series of radiographs, preferably including a pre-exposure baseline film, greatly assists in the interpretation of changes thought to be consistent with asbestos-related diseases which can be assessed developmentally over a given, known, time period.

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 7 of 34 asbestosclaims.law/library/17543/7

exposure presents little diagnostic difficulty. It is possible for a patient with asbestos induced pleural disease to develop a nonspecific interstitial fibrosis but this is generally regarded as uncommon. The difficulty with the use of the chest roentgenogram relates to the detection of lesser degress of 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 roentgenologic involvement in the pneumoconioses was developed by the International Labour Organization; and is currently called the ILO-1980 Classification (38). 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 called p, q, and r respectively. 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 opacifications and they are called s, t, and u, respectively.

A02190

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 8 of 34 asbestosclaims.law/library/17543/8

The number of these abnormalities in a given area of the chest x-ray, 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. If, however, 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 reliabilitly (i.e., in terms of reproducibility) was considerably improved. This method of giving the observer two options (the one he thought most likely, and next most likely) 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 the normal roentgenologic 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 highly subjective and that numerous causes of such roentgenologic shadowing other than

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Diag... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 9 of 34 asbestosclaims.law/library/17543/9

asbestosis exist. Accordingly, criteria other than roentgenographic ones have been sought. To evaluate the usefulness of a given test used as a criterion for asbestos, the results of the test need to be known in unexposed persons who are similar in age, sex, race, smoking habits, geographic location, other environmental exposures and socioeconomic status. Information is often scanty in this regard particularly since few longitudinal studies are available to examine the variability of criteria that are indicative of early interstitial fibrosis. Information is available on some and will now be reviewed.

A02192

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 10 of 34 asbestosclaims.law/library/17543/10

Microscopic Appearances

There is little information on the early pathophysiology of asbestosis in humans. Current opinion is largely based on inferences from animal studies. The initial reaction in the interstitial tissue is believed to resemble 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 (33, 34). The process is believed to be concentrated initially in peribronchiolar regions (10, 29). The initial lesion is a bronchiolar wall thickened by the accumulation of collagen and reticulin. Metaplasia of the squamous and epithelial cells often occurs. Alternatively there may be cuboidalization of the epithelial cells. Characteristically, in early stages, only an occasional pulmonary subunit is involved. More advanced cases show a diffuse fibrosis, involving the interstitium, frequently associated with areas of solid fibrosis where laminated collagen may replace the entire parenchyma. Such areas may also show alveolar cell hyperplasia and sclerosis of vessel walls (29). (The presence of numerous

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 11 of 34 asbestosclaims.law/library/17543/11

uncoated and coated asbestos or ferruginous bodies is an important feature confirming asbestos exposure.)

Before a pathologic diagnosis of asbestosis can be made a variety of considerations must be taken into account including the following:

1. There are numerous other causes of interstitial fibrosis.

2. The distribution of interstitial fibrosis in asbestosis may be spotty, and therefore, adequate sampling of the lung must be done. The lingular and the right middle lobe are particularly prone to nonspecific fibrosis and sampling must take this into consideration.

3. While advanced asbestosis characteristically shows numerous asbestos bodies, this may not always be true because fibers are cleared from the lungs and undergo dissolution and fragmentation with time (31). Thus, in some cases it may be difficult to demonstrate fibers. In our opinion this is rare.

4. The absence of a history of asbestos exposure removes the diagnostic certainty, but the presence of numerous asbestos bodies, in excess of those found in the lungs of the "non-exposed populations" may lend credence to a diagnosis of asbestosis.

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 12 of 34 asbestosclaims.law/library/17543/12

The Pneumoconiosis Committee of the American Pathologists and the National Institute for Occupational Safety and Health dealt with these considerations when formulating the following statement with which we concur. "The criteria that permit the pathologist to establish the diagnosis of asbestosis have evolved during a review of many cases of the disease. Presently, the minimal features that permit the diagnosis are the demonstration of discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies. These morphologic findings, although adequate to establish the diagnosis of asbestosis in an early evolutionary stage, have not been shown to result in functional and radiologic alterations. The demonstration of asbestos bodies in the absence of fibrosis is insufficient evidence to justify the diagnosis of asbestosis. Conversely, a definite diagnosis of asbestosis can not be made by the pathologist in cases that show characteristic fibrosis in the absence of asbestos bodies or other evidence of fibers. Because asbestos bodies are unevenly distributed in tissue, an adequate number of samples should be examined thoroughly.

In the lesions, asbestos bodies are located either in the walls of the bronchioles or in the air spaces, where they are

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 13 of 34 **asbestosclaims.law/library/17543/13**

often closely associated with macrophages. When only a single asbestos body is found in a histologic section, it is necessary to demonstrate additional bodies or uncoated fibers (either in deeper sections of the same block or in other samples of tissue) to establish the diagnsosis of asbestosis"(31).

They further state that "although the demonstration of asbestos fibers by the electron microscopic study of tissue digestates provides evidence of exposure, ultrastructural technique can not be used to establish definitively the etiologic role of asbestos in disease."(31)

This Committee has published guidelines for methods of assessing lung fiber concentration and pathologic grading of asbestosis. The certainty of the cause and effect relationship of asbestos to the fibrotic process increases with increasing numbers of such particles and fibers visualized by light microscopy. Electron-microscopy of proven cases shows very large numbers of uncoated and very fine particles and fibres (35).

Since asbestos bodies and fibers appear in lungs without evidence of asbestos related disease, the question arises as to how many such bodies are necessary to infer a cause and effect relationship between asbestos particles and fibrosis. No

A02196

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 14 of 34 asbestosclaims.law/library/17543/14

precise answer exists, but efforts to quantify the numbers of asbestos particles in known cases indicate that it is high. In the cases of asbestosis studied by Whitwell, the lungs nearly always showed three million light visible fibers per gram, control lungs generally showing less than 20,000 fibers per gram (36).

The meaning of particles and fibers visualized by electron-microscopy, when few or none are visualized by light microscopy, awaits further epideniologic and pathologic evaluation. However, asbestos fibers seen only by electron microscopy certainly mean that exposure has occurred. What is not known with precision at this time is the number of fibers that are present in the lungs of persons in the general population. The accuracy of estimation of the total lung burden of asbestos assessed by electron-microscopy has not been carefully delineated.

~~Chrysotile~~, ~~a~~ A lung containing a million chrysotile fibers per gram of dry tissue is believed to be consistent with the background exposure of the general population. In contrast, a lung containing a million fibers of amosite of crocolite per gram has been considered to reflect a substantial occupational exposure to asbestos dust. (Churg A.; Fiber counting and analysis in the

AU2197

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 15 of 34 asbestosclaims.law/library/17543/15

diagnosis of asbestos related disease. Hum Pathol 1982, 14: 381-92). An electron microscopic field, of necessity, represents a small sample of the lung and analysis of multiple fields are required to reflect the true asbestos lung burden. In our opinion, additional studies need to be done on the prevalence of the various asbestos fiber types and their variation in the lungs of normals and persons with various asbestos related diseases. ~~need to be done.~~

Clinical Diagnosis

In the usual clinical setting, the diagnosis of asbestosis has to be made ~~in the absence~~ without the benefit of lung tissue to examine. Open lung biopsy is ~~rarely~~ contra-indicated ~~for assessing~~ in the assessment of workers for compensation purposes. The benefit of the doubt should be given whenever the clinical features and occupational exposure data are compatible with the diagnosis. Indeed, when ~~it~~ a biopsy is done, careful attention must be paid to the sampling considerations mentioned above and the surgical technique employed (37). In most instances, the clinician and epidemiologist must still rely on indirect methods of diagnosing asbestosis. The diagnosis is based on correlations with observations from pathologically proven cases.

Diagnosis of asbestosis does not mean that ~~either any~~ measurable impairment of lung function or physical ~~dis~~ disability is always present and compensation awarded should therefore always be a matter of judgement based upon the demonstrated clinical and physiologic features of the individual case.

A02198

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 16 of 34 asbestosclaims.law/library/17543/16

Dyspnea

Asbestosis has been described as a monosymptomatic disease, dyspnea being the major complaint of the affected individual (39). There is no doubt that shortness of breath is common and troublesome in individuals with clinically significant interstitial fibrosis, but in early cases may not be present a significant symptom. Dyspnea, however, is common in many other cardiopulmonary disorders and is particularly ~~subject to~~ influenced by emotional factors which are likely to be ~~relevent~~ prevalent in instances of suspected industrially related disease. Accordingly, it is not useful to use dyspnea alone as scientific evidence ~~of~~ for the presence of asbestosis.

Clubbing

Clubbing of the fingers occurs in many of the diagnosed cases of pulmonary asbestosis and can be quantified objectively. It occurs more commonly in asbestos exposed workers than controls (40, 41, 42). The diagnostic usefulness of clubbing is limited, however, by two important considerations. First, there are many other causes of clubbing including congenital clubbing, heart disease, liver disease and other lung diseases. Secondly, clubbing when present, is a late finding in pulmonary asbestosis (43). Thus, since the majority of persons with significant pulmonary fibrosis do not have clubbing and ~~that~~ many asbestos workers with clubbing may have it for reasons other than pulmonary fibrosis, the diagnostic usefulness of clubbing is limited.

A0219

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 17 of 34 asbestosclaims.law/library/17543/17

Basilar Crackles

Crackles have been recognized as a feature of asbestosis for over 50 years and have been believed by many to be an early finding (44, 45, 46). They have been described as characteristic in their sound ("fine," "cellophane," "velcro," "close to the ear") and in their distribution (bilateral, basal) (47). They differ in quality and timing from the crackles of bronchitis which tend to be fewer in number, more medium in quality and earlier in timing. Bronchitic crackling begins with the beginning of inspiration and usually discontinues prior to mid or late inspiration. 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 toward the posterior bases. As the disease advances, the crackles become distributed at progressively higher levels up from the bases (47). They are often difficult to distinguish from the crackles of congestive heart failure. Reported rates vary, but about half of the persons considered to have asbestosis on clinical grounds have crackles (44, 48, 49, 50); prevalences in exposed population range from about 10-20%. Such prevalences depend on duration of exposure, the age of the population, and

A02200

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 18 of 34 asbestosclaims.law/library/17543/18

prevalence of other diseases causing fine crackles. Observer variability exists in chest auscultation, but this can be reduced by training and waveform analysis (51, 52, 53). In summary, under carefully controlled circumstances crackles can be useful in diagnosing interstitial fibrosis. They do not appear to be specific, however, for the interstitial fibrosis related to asbestos.

A02201

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia… Published by AsbestosClaims.Law
ACL Doc 17543 · Page 19 of 34 **asbestosclaims.law/library/17543/19**

Diffusing Capacity

The Carbon Monoxide Diffusing capacity (DL_{CO}) (or transfer factor) has been the subject of numerous studies with somewhat conflicting results. In most population studies or normal studies it is lower in asbestos exposed workers than in normal controls although not always at a statistically significant level (41, 42, 54, 55, 56). There is not always a clear relationship to dust exposure indices (57, 58). It has, however, been shown to correlate with the severity of the histologic lesion in interstitial fibrosis (59), and its reduction can precede roentgenologic abnormalities. At this time a reduction of the diffusing capacity in an asbestos worker, in the absence of other known causes for impaired gas exchange, would provide evidence for asbestosis, but further study is necessary to elucidate its precise role.

OTHER STUDIES

Diagnostic radiographic studies have been employed for monitoring persons exposed to asbestos. A reduction in roentgenologic lung volume appears promising, since it is applicable to serial studies of patients, but it requires careful control of inspiration. This approach has not yet been taken in a large number of subjects exposed to asbestos.

A02202

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 20 of 34 asbestosclaims.law/library/17543/20

Lung volume is also highly correlated with total lung capacity measured by the helium dilution technique or body plethysmography. Inspiratory capacity was shown by Becklake et al. to be suitable for surveillance of workers, but is not likely to add much more information than vital capacity (VC), as the two tests are highly correlated (61). Evidence has been presented that increased elastic recoil, in asbestos exposure and in intersitial fibrosis not associated with asbestos, has a peribronchial rather than an alveolar location (62, 63). This finding suggests that tests for small airways disease ~~might~~ may in the future be applicable to early detection (62). In one study, neither closing volume nor closing capacity correlated with the duration of exposure or with the asbestos-dust index (64). Gallium scanning, ventilation perfusion scanning, bronchoalveolar lavage, and transbronchial biopsy need further evaluation with respect to their usefulness in diagnosing asbestosis. CT scanning offers the advantage of aiding in the differentiation of pleural from parenchymal disease. The value of CT scanning in the detection of interstitial fibrosis also needs to be further evaluated. Thus, at this time, criteria other than bilateral basal inspiratory crackles, restrictive lung function ~~a~~ abnormality, reduced carbon monoxide diffusing capacity of the lung (DL_{CO}), and roentgenogram consistent with interstitial fibrosis

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 21 of 34 asbestosclaims.law/library/17543/21

of profusion of irregular opacities greater than 1/0 (ILO u/c, 1980) ~~of 1/2 or 1/1~~ are either impractical, of unproven value, or are not likely to yield additional information because of their high correlation with one of these four. In our opinion, combinations of these abnormalities are more reliable in terms of specificity, relation to duration of exposure, consistency, and predictive value. Surprisingly, little work has been carried out on combinations of abnormalities. Even the investigators who employed sophisticated statistical techniques have not specifically reported on them.

COMBINATIONS of the features described above useful if relied upon as illustrative of the ~~Such~~ Combinations are not likely to prove ~~to show the~~ on the grounds of chance alone, so-called earliest change in asbestosis. Intuitively one test is likely to become noticeably abnormal first. It is likely that the first abnormality is not always the same one (e.g., one worker may have only abnormal Dsb (single breath diffusing capacity), and another only crackles ~~rales~~ as the first manifestation). This has been demonstrated with respect to restrictive lung function pattern and reduced DL_{CO}(65). It is likely that observations will have to be made in large groups of exposed persons over long periods of time to delineate clearly the best single test for early diagnosis of asbestosis if, indeed, a single initial pathway exists.

AU2204

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 22 of 34 asbestosclaims.law/library/17543/22

DIFFERENTIAL DIAGNOSIS

Streaky densities on chest x-ray consistent with a parenchymal disease have many causes, numbering about 125 according to Jánower and Blennerhasset (66). Some of the more common ones are summarized in Table 1. Skin changes, Raynaud's phenomenon, and esophageal symptoms point toward the diagnosis of progressive systemic sclerosis. Likewise, skin rash, positive lupus erythematosus cell test, positive test for antinuclear antibodies, or evidence of polyserositis suggest the diagnosis of systemic lupus erythematosus. A lupus-like syndrome due to a drug (hydralazine and procainamide) must also be excluded, usually by the medical history. Although sarcoidosis can produce a severe restrictive defect with parenchymal opacification, clues in the form of commonly asociated features, such as a history of hilar lymphadenopathy, hypercalcemia, or uveitis are helpful. Polyarteritis nodosa and eosinophilic granuloma are usually readily distinguished.

The roentgenographic appearance of miliary tuberculosis is usually quite different from that of asbestosis. A viral pneumonia is more difficult to distinguish roentgenographically but history of the onset of the illness with a fever or flu-like syndrome or the presence of an associated epidemic is helpful.

A02205

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 23 of 34 asbestosclaims.law/library/17543/23

Congestive heart failure can produce fine crackles, restrictive lung function pattern and reduced DL_{co} as well as nonspecific irregular opacifications on roentgenogram. It is usually easily excluded by history or physical examination. Chronic obstructive pulmonary disease (COPD) presents more of a problem. Irregular opacifications, such as seen in asbestosis, are not so prominent a feature of COPD. Bullae and over-distended lung fields also are not features of asbestosis. The FEV1:FVC ratio helps distinguish between the two diseases, but certainly obstructive lung disease and asbestosis may coexist. The relative importance of cigarette smoking and asbestos in the development of the combined problem of restrictive and obstructive disease may be difficult or even impossible to assess.

Since an unusual feature of asbestos exposure is bilateral pleural thickening, the question arises as to the helpfulness of such thickening in indicating that a patient with pulmonary fibrosis has asbestosis. Indeed, asbestos appears to be a rather potent stimulus for the development of pleural abnormalities. Selikoff found pleural fibrosis in 65% of persons he studied 40 years ~~from the onset of~~ after their initial exposure to asbestos. ~~With~~ In patients with no known exposure to

A02206

UCC 023759

Published by AsbestosClaims.Law
asbestosclaims.law/library/17543/24

asbestos, or other known hazardous materials (67), the question arises as to whether ~~that~~ an indirect or occult exposure to asbestos might have caused the pleural thickening. Severe pleural thickening is not common even after ~~in~~ asbestos exposure. It was present in only 2.5% of the asbestos workers studied by Selikoff. Since there were no controls in that study, it is difficult to be certain that asbestos was the cause of the pleural fibrosis in those subjects. Indeed, Gilson reported in 1969 that pleural thickening was found in 187 of 3860 routine roentgenograms of the chest in Great Britain (68). He conducted one of the few objective studies of pleural thickening by comparing the asbestos exposure of 113 of the 187 subjects with that of 113 age and sex matched controls. He found "a slight but unimpressive excess of positive histories of exposure to asbestos among the cases." Thus, it is not necessary to assume an occult exposure to asbestos in every instance of pleural thickening; the presence of pleural thickening is not definitive evidence of asbestos exposure. Other causes, such as other dusts and residual from infections, are almost as common. In contrast to the relatively nonspecific finding of pleural thickening, the demonstration of hyaline or calcified pleural plaques, usually bilateral and symmetrical, ~~or calcification~~ is better evidence of asbestos exposure.

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 25 of 34 asbestosclaims.law/library/17543/25

Unfortunately, the latter usually occurs only many years after the onset of the exposure, thus limiting usefulness for early diagnosis.

A major problem exists in the differential diagnosis when more than one disease is present, whether it is congestive heart failure, COPD, or other chronic lung disease. There are diseases unrelated to asbestos exposure but with similar symptoms, and these do occur in some persons with asbestos exposure. Absence of a clear history of exposure to asbestos makes distinguishing ~~diagnosing~~ diffuse interstitial fibrosis from other sources almost impossible. Fortunately, significant degrees of interstitial fibrosis are rare in the general population. The prevalence of lesser degress of interstitial fibrosis is not well known and considerable caution has to be exercised in attributing all such phenomena to asbestos exposure, either known or occult.

In summary, in assessing an individual ~~be~~ for asbestosis a variety of tests have value. In the absence of microscopic study of lung tissue no single examination on its own can be considered pathognomonic. The greater the number of abnormal criteria, the more likely that asbestosis is present, but other illnesses need to be carefully excluded.

A02208

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 26 of 34 asbestosclaims.law/library/17543/26

The diagnosis of interstitial fibrosis was discussed with this degree of detail because it is at the core of the attributability of illness to asbestos. When significant asbestosis is present there is little difficulty with the cause and effect relationship. Conversely, the certainty of attributing decreases with decreasing evidence of asbestosis.

A02204

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia… Published by AsbestosClaims.Law
ACL Doc 17543 · Page 27 of 34 **asbestosclaims.law/library/17543/27**

TABLE I:

Some Diseases To Be Considered in the

Differential Diagnosis of Asbestosis

Congestive Heart Failure

Chronic Obstructive Pulmonary Disease

Interstitial Fibrosis

Progressive Systemic Sclerosis

PSS	Eosinophilic granuloma
Lupus	Miliary tuberculosis
Hydralazine	Viral pneumonia
Procainamide	Rheumatoid
Sarcoidosis	Idiopathic

Polyarteritis nodosa

Interstitial Fibrosis plus Pleural Thickening

Rheumatoid lung

Blastomycosis, other fungi

Drug induced

Other pneumoconiosis (e.g. talc)

Silica

A02210

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 28 of 34 asbestosclaims.law/library/17543/28

REFERENCE LIST

1. Hamilton, A & Hardy, H: Industrial Toxicology. ed.3, Publishing Sciences Group Inc., Acton, Mass. 1974, p. 421.

2. Gilson, GC: Asbestos cancer: Past and future hazards. Proc R Soc Med, 1973, 66, 395.

3. Zussman, J: Asbestos: Nature and history. Rev. Ciba Geigy, 1972, 2, 3.

4. Smither, WJ: Asbestos and asbestosis. Ann Occup Hyg, 1970, 13, 3.

5. Biological effects of asbestos. Selikoff. IJ & Churg, J, Co-chairmen, Proceedings of a conference held at the New York Academy of Sciences, Oct. 19-21, 1964, Ann N Y Acad Sci, 1965, 132, pp. 1-766.

6. Biological effects of asbestos. Anspach, K, Chairman, Deutsches Zentralinstitut fur Arbeitsmedizin: Gesellschaft fur Arbeitshygiene und Arbeitsschutz in der DDR, Dresden, April 22-25, 1968, pp. 1-312.

7. Biological effects of asbestos. Bogovski, P; Gilson, JG; Timbrell, V & Wagner, JC, eds. Proceedings of a working conference at IARC, Lyon, October 2-6, 1972, IARC Scientific Publications, No. 8, Lyon, 1973, pp. 1-341.

8. Proceedings of the Pneumoconiosis Conference. Johannesburg, South Africa, February 1959, Orenstein, AJ, ed., J and A Churchill Ltd., London 1960, pp. 1-629.

9. Pneumoconiosis. Shapiro, HA, ed., Proceedings of the International Conference, Johannesburg, South Africa, 1969, Oxford University Press, Cape Town, 1970, pp. 3-645.

10. Parkes, WR: Asbestos-related disorders. Brit J Dis Chest, 1973, 67, 261.

11. Steil, PM & McGill, T: Asbestos and laryngeal carcinoma. Lancet, 1973, 2, 416.

12. Newhouse, ML & Berry, G: Asbestos and laryngeal carcinoma. Lancet, 1973, 2, 615.

13. Libshitz, HI; Wershba, HS; Atkinson, GW & Southard, HE: Asbestos and carcinoma of the larynx, JAMA, 1974, 228, 1571.

A02211

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 29 of 34 asbestosclaims.law/library/17543/29

14. Guidotti, TL; Abraham, JL & DeNee, PB: Asbestos exposure and cancer of the larynx. West J Med, 1975, 122, 75.

15. Graham, J & Graham, R: Ovarian cancer and asbestos. Environ Res, 1967, 1, 115.

16. Doniach, I; Swettenham, KV & Hathorn, MKS: Prevalence of asbestos bodies in a necropsy series in East London: Association with disease, occupation, and domiciliary address, Br J Ind Med, 1975, 32, 16.

17. Weiss, W: Clinical epidemiology. Arch Environ Health, 1970, 20, 5.

18. Speil, S & Leineweber, JP: Asbestos minerals in modern technology, Environ Res, 1969, 2, 166.

19. Wright, GW: Asbestos and health in 1969, Am Rev Resp Dis, 1969, 100, 467.

20. Harries, PG: Asbestos dust concentrations in ship repairing: A practical approach to improving asbestos hygiene in naval dockyards, Ann Occup Hyg, 1971, 14, 241.

21. Respiratory Diseases: Task Force Report on Problems, Research Approaches, Needs. The Lung Program, National Heart and Lung Institute, October 1972, U.S. Department of Health, Education and Welfare.

22. Lee, CL & Smith, DJ: Steelwork insulated with sprayed crocidolite asbestos: Controlling a potential hazard. Ann Occup Hyg, 1974, 17, 49.

23. Neurman, L: Asbestos bodies and pleural plaques in a Finnish series of autopsy cases. Acta Patnol Microbiol Scand, 1966, (Supplement 181, p. 8).

24. Mattson, SB & Ringqvist, T: Pleural plaques and exposure to asbestos, Scand J Respir Dis, 1970 (Supplement 75, p. 4).

25. Lewinsohn, HC: Early malignant changes in pleural plaques due to asbestos exposure: A case report. Brit J Dis Chest, 1974, 68, 121.

26. Roberts, GH: The pathology of parietal pleural plaques. J Clin Path, 1971, 24, 346.

27. Mourihane, D O'B; Lessof, L & Richardson, PC: Hyaline and

A02212

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 30 of 34 asbestosclaims.law/library/17543/30

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. Brit Med J, 1965, 1, 1609.

29. Le Bouffant: [illegible] effects of asbestos. [illegible], P; Gibbon, JC & [illegible], [illegible], [illegible]. [illegible] of a working conference at IARC, Lyon, October 2-5, IARC Scientific Publications, No. 8, Lyon, 1974, 249.

30. [illegible], [illegible], [illegible]: Pathological aspects of asbestosis. Postgrad Med J, 1966, 42, 615.

30. Heard, BE & Williams, R: The pathology of asbestosis with reference to lung function. Thorax, 1961, 16, 264.

31. The Pathology of Asbestos-Associated Diseases of the Lungs and Pleural Cavities: Diagnostic criteria and proposed grading schema. Craighead, JE, Chairman, Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. Arch Pathol Lab Med, 1982, 106, 544.

32. Solomon, A; Goldstein, B; Webster, I & Sluis-Cremer, GK: Massive fibrosis in asbestosis. Environ Res, 1971, 4, 430.

33. Gaensler, EA & Kaplan, AI: Asbestos pleural effusion. Ann Intern Med, 1971, 74, 176.

34. Gaensler, EA; Carrington, CB; Coutu, RE; Tomasian, A; Hoffman, L & Smith, AA: Pathological, physiological and radiological correlations in the pneumoconioses. Ann N Y Acad Sci, 1972, 200, 574.

35. Miller, A; Langer, AM; Tierstein, AS & Selikoff, IJ: "Nonspecific" interstitial pulmonary fibrosis: Association with asbestos fibers detected by electron microscopy. N Engl J Med, 1975, 292, 91.

36. Whitwell,F; Scott, J & Grimshaw, M: Relationships between occupations and asbestos fibre content of the lungs in patients with pleural mesothelioma, lung cancer and other diseases. Thorax, 1977, 32, 377-86.

37. Gaensler, EA & Carrington, CB: Open biopsy for a chronic diffuse infiltrative lung disease: Clinical, roentgenographic and physiological correlations in 502 patients. Ann Thorac Surg, 1980, 30, 411-426.

A02213

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 31 of 34 asbestosclaims.law/library/17543/31

38. International Labour Office. Guidelines for the Use of ILO International Classification of Radiographs of Pneumoconioses. Rev. Ed. 1980. Occupational Safety and Health Series. No. 22, International Labour Office, Geneva, 1980.

39. Selikoff, IJ; Churg, J; Hammond, EC: The occurrence of asbestosis among insulation workers in the United States. Biological Effects of Asbestos, Ann N Y Acad Sci, 1965, 132, 139.

40. Kleinfeld, M; Massite, J; Kooyman, O et al: Effect of asbestos dust innalation on lung function. Aren Environ Health, 1966, 12, 741.

41. Regan, GM; Tagg, B; Walford, J et al: The relative importance of clinical, radiological and pulmonary function variables in evaluating asbestosis and chronic obstructive airway disease in asbestos workers. Clin Sci, 1971, 41, 569.

42. Wallace, WFM & Langlands, JHM: Insulation workers in Belfast. Comparison of a random sample with a control population. Br J Ind Med, 1971, 28, 211.

43. El-Sewefy, AZ; Awad, S & Abdel-Salam, MS: Chest symptomatology in an Egyptian cement-asbestos pipe factory (a field survey). J Egypt Med Assoc, 1970, 53, 84.

44. Epler, GR; Gaensler, EA & Carrington, CB: Crackles (rales) in the interstitial pulmonary diseases. Chest, 1978, 73, 333-339.

45. Shirai, F; Kudon, S; Shubuya, A; Sada, K & Mikami, R: Crackles in asbestos workers: Auscultation and lung sound analysis. Br J Dis Chest, 1981, 75, 386-396.

46. Elmes, PC: Health parameters other than mesothelioma. Proceedings of Asbestos Symposium, Johannesburg, South Africa, October 3-7, 1977, National Institute for Metallurgy, Randburg, 1978, 9-16.

47. Smither, WJ: Secular changes in asbestosis in an asbestos factory. Biological Effects of Asbestosis. Ann N Y Acad Sci, 1965, 132, 166.

48. Rossiter, CE & Berry, G: The interaction of asbestos exposure and smoking on respiratory health. Bull Europ Physiopath Resp, 1978, 14, 197-204.

49. Huuskonen, MS: Clinical features, mortality and survival

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 32 of 34 asbestosclaims.law/library/17543/32

of patients with asbestosis. Scand J Work Environ & Health, 1978, 4, 265-274.

50. Segarra, F; Baselga, MM; Lopes, IP & Perez, MJ: Asbestosis in a Barcelona fibrocement factory. Environ Research 1980, 23, 292-300.

51. Workum, P; Del Bono, EA; Holford, SK & Murphy, RLH: Accuracy of a technician in chest auscultation for crackles. Submitted for publication to Am Rev Resp Dis, Feb. 1983.

52. Murphy, RLH; Gaensler, EA; Holford, SK; Del Bono, EA & Epler, GR: Crackles in the early detection of asbestosis. Tentatively accepted for publication in Am Rev Resp Dis, August 1982.

53. Murphy, RLH; Holford, SK & Knowler, WC: Visual lung sound characterization by time-expanded wave-form analysis. New Engl J Med, 1977, 296, 968-971.

54. Murphy, RLH; Ferris, BG; Burgess, WA et al: Effects of low concentrations of asbestos. Clinical, environmental, radiologic and epidemiologic observations in shipyard pipe coverers and controls. N Engl J Med, 1971, 285, 1271.

55. Murphy, RLH; Gaensler, EA; Ferris, BG; Fitzgerald, M; Solliday, N & Morrisey, W: Diagnosis of "Asbestosis". Observations from a longitudinal survey of shipyard pipe coverers. Am J Med, 1970, 65, 466-498.

56. Langland, JAM; Wallace, W & Simpson, H: Industrial workers in Belfast. 2. Morbidity in men still at work. Brit J Ind Med, 1971, 28, 217.

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

58. Murphy, RLH & Sorenson, K: Chest auscultation in the diagnosis of pulmonary asbestosis. J Occup Med, 1973, 15, 272.

59. Chiappino, G. & Zedda, S: Value and significance of some diagnostic parameters in workers exposed to asbestos. Securitas Anno (Italy), 1973, 56, 841.

60. Reger, RB; Young, A & Morgan, WKC: An accurate and rapid method of determining total lung capacity. Thorax, 1972, 27, 163.

A02215

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 33 of 34 asbestosclaims.law/library/17543/33

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

62. Jodoin, G; Gibbs, GW; Macklem, PT et al: Early effects of asbestos exposure on lung function. Am Rev Resp Dis, 1971, 104, 525.

63. Ostrow, D & Cherniack, RM: Resistance to airflow in patients with diffuse interstitial lung disease. Am Rev Resp Dis, 1973, 108, 205.

64. Konietzko, N; Gerke, E; Schlehe, H et al: Closing volume in workers exposed to asbestos (German). Prax Pneumol, 1974, 28, 829.

65. Thomson, ML; McGrath, MW; Smither, WJ et al: Some abnormalities in measurement of pulmonary diffusion in asbestosis with chronic bronchitis and emphysema. Clin Sci, 1961, 21, 1.

66. Janower, ML & Blennerhassett, JB: Lymphagitic spread of metastatic cancer to the lung. Radiology, 1971, 101, 267-273.

67. Selikoff, IJ: The occurrence of pleural calcification among asbestos insulation workers. Biological effects of Asbestos. Ann N Y Acad Sci, 1965, 132, 351-367.

68. Gilson, JC: Asbestos Health Hazards: Recent observations in the United Kingdom, Proceedings of the International Conference on Pneumoconiosis, Johannesburg, South Africa, London, Oxford University Press, 1969.

A02216

Union Carbide trial exhibit UC-2584: R. L. H. Murphy, M.D., Draft Report 'Asbestos Criteria' on Health Effects, Dia... Published by AsbestosClaims.Law
ACL Doc 17543 · Page 34 of 34 asbestosclaims.law/library/17543/34