A LAWYER'S VIEW OF ASBESTOS MEDICINE: DIAGNOSIS AND CAUSATION OF MESOTHELIOMA, LUNG CANCER, ASBESTOSIS, AND OTHER DISEASES

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Diseases which are related to or at least alleged to be related to asbestos exposure can be divided into five categories: mesothelioma, lung cancer, other cancers, asbestosis, and pleural thickening-plaques.

Mesothelioma

Many organs of the body are surrounded by a mesothelial lining. This lining is two rows of cells which secrete a fluid between the cells which serves as a lubricant. Without such lining the organs would rub against muscle, bone, and other tissues causing pain and damage. There is a pleural lining around the lungs and a peritoneal lining around the abdominal organs. Even the heart has a mesothelial lining called the pericardial lining.

Malignant mesothelioma is a tumor that arises in the mesothelial cells of this lining. Hence, mesothelioma occurring in the abdomen is called peritoneal mesothelioma. Mesothelioma occurring in the chest cavity is called pleural mesothelioma.

Mesothelioma is a rare tumor occurring in approximately one to two persons per million population. Exposure to asbestos has substantially increased the occurrence of mesothelioma. In fact, the occurrence of mesothelioma has been used as a marker for asbestos exposure. Although asbestos causes many cases of mesothelioma, there are other known causes of mesothelioma, such as erionite in Turkey and radiation. Viruses and inflammation have also been listed as causes of mesothelioma. However, smoking does not cause mesothelioma.

There are two principal types of mesothelioma depending upon the appearance of the cells upon microscopic review by the pathologist. These types are called epithelial and sarcomatous. Both forms of mesothelioma are uniformly fatal. However, sarcomatous mesothelioma on the average proceeds more aggressively and causes death even earlier than epithelial mesothelioma. One study showed that most persons with mesothelioma were dead within one year of diagnosis or onset of symptoms, with the vast majority dead within two years and all persons in the study dead within three years. There are few cases of long term survivors of mesothelioma, but many doctors suspect that such tumors were in fact misdiagnosed as malignant mesothelioma. Long survival of a person with mesothelioma suggests the tumor in fact may not be mesothelioma. Treatment of mesothelioma is seldom, if ever, undertaken as an attempt to cure the patient. Treatment is rather directed toward the patient's comfort and possibly modest increases in his longevity. A select few patients are eligible for an operation called an extrapleural pneumonectomy with survival approaching five year for 50% of patients.

Mesothelioma is a diagnosis principally reserved to pathologists. Clinically, a person may have weight loss, shortness of breath, fluid in the body cavity affected, pain, and other symptoms. However, other cancers and even some benign conditions can cause such symptoms. Pathologists can use a number of methods to diagnose mesothelioma. The gross appearance of a mesothelial tumor is often many nodules studding or a sheet of tumorous material encasing the lungs or abdominal organs as the tumor grows throughout the pleural or peritoneal lining. Even though this is the most characteristic growth pattern of mesothelioma, any number of primary and metastatic tumors can invade the pleural and peritoneal lining and grow in this manner. In fact although mesothelioma may be the single tumor that most often grows in this manner, mesothelioma is actually a minority of all of the tumors that can grow in this manner.

The pathologist will also look at the cells under a microscope to see if these malignant cells show the typical characteristics of a mesothelioma. In some instances

this microscopic review allows a clear diagnosis. In other instances the pathologist cannot render a certain opinion from his microscopic examination. Finally, cells on microscope slides can be stained with different materials to see if the cells react creating various staining patterns. This staining provides a better basis for diagnosis in some types of mesothelioma than others. Although such staining is not an exact science and does not provide a guaranteed diagnosis, some stains can be diagnostic that a particular tumor likely is or is not mesothelioma.

Frequently used immunohistochemical staining for the diagnosis of mesothelioma and particularly to distinguish mesothelioma from adenocarcinoma of the lung include the following:

Stain positive if the tumor is mesothelioma

- CK 5/6
- Pancytokeratin (AE1/AE3) and other keratin stains
- WT-1
- HBME-1
- Calretinin
- Mesothelin
- EMA
- D2-40
- Vimentin
- N-cadherin

Stain negative if the tumor is mesothelioma

- TTF-1
- MOC-31
- CEA
- B72.3
- BerEp4
- Desmin
- S-100

- LeuM1 (CD15)
- Mucin after digestion with diatase

Important notes regarding such staining include the following:

- The appearance of the cells and their organization under the microscope, called "histology," is just as important as the results of the immunohistochemical staining.
- No single stain or group of stains is diagnostic of mesothelioma with certainty, e.g. D2-40 is positive in lymphatic tissue and in lymphovascular tumors, seminomas, and hemangioblastomas.
- Immunohistochemical staining is more reliable for epithelial mesothelioma than for sarcomatoid mesothelioma.
- Whether a stain is actually positive depends upon what part of the cell stains positive, e.g. WT-1 must stain the nucleus to be considered positive.
- Whether a stain is actually positive also depends upon the percentage of the tumor cells that stain positive, e.g. the mention of "focal" staining in many pathology reports may not be a true positive.
- Research shows that if two positive and two negative stains are selected, the most reliable stains for epithelial mesothelioma are +CK 5/6 and +WT-1 and –TTF-1 and –MOC-31.

It is disputed whether there is actually a safe level of exposure to asbestos which will not cause mesothelioma. Regardless, many experts testify that they are not able to identify any safe or tolerable level of exposure. For relatively recent epidemiological work suggesting that low levels of exposure will cause mesothelioma, see LaCourt, A. et al, "Attributable Risk in Men in Two French Case-Control Studies on Mesothelioma and Asbestos" European Journal of Epidemiology 25:799 (2010). For a defense lawyer's view in refutation, see the publication by Zellmer for the St. Louis asbestos conference for NBI Publications in 2011.

Asbestos of course is not a single mineral but a number of fibrous minerals divided into two groups, serpentine and amphibole. Chrysotile is a serpentine while crocidolite, amosite and tremolite are amphibole asbestos. It is beyond the scope of this work to resolve the dispute regarding whether chrysotile asbestos actually causes mesothelioma; however, without evaluation of the merits of each position, a delineation of the positions on this issue, and there are a number of different positions, would be in order:

- Pure chrysotile will not under any circumstances cause mesothelioma;
- Chrysotile is only weakly causative of mesothelioma, such that there are only a few cases of mesothelioma among persons only exposed to pure chrysotile;
- The risk that chrysotile, amosite and crocidolite can cause mesothelioma is expressed as a ratio of 1:100:500 respectively.
- Tremolite contamination of the chrysotile causes mesothelioma, but there is essentially no such thing as chrysotile not contaminated by tremolite;
- Although chrysotile alone may not cause mesothelioma, in combination with amphiboles, it in fact causes mesothelioma;
- Chrysotile may cause pleural mesothelioma but will not cause peritoneal mesothelioma;
- Chrysotile is just as capable of causing mesothelioma as amphiboles.

Corbett McDonald finds from work with digestion of lung tissue that the risk of mesothelioma from chrysotile is likely little or none. See "Epidemiology of Mesothelioma-An Outline" in Annals of Occupational Medicine vol.54, no. 8 p. 851 (2010). The article by Ken Donaldson et al "Asbestos, Carbon Nanotubules and the Pleural Mesothelium: A Review of the Hypothesis Regarding the Role of Long Fiber Retention in the Parietal Pleura" in Particle and Fibre Toxicology 7:5 (2010) explains the physiology of why only long fiber amphiboles cause mesothelioma, i.e. that only long fibers can block the clearance of fibers from the parietal pleura into the lymph system. Contrast Yano E, Wang ZM, et al. "Cancer Mortality Among Workers Exposed to Amphibole-Free Chrysotile Asbestos" American Journal of Epidemiology 154:538-543

(2001) (heavy exposure to chrysotile alone with negligible amphibole contamination causes lung cancer and mesothelioma).

Most plaintiffs' experts will opine that any exposure above background levels of asbestos in the air is sufficient to contribute to cause mesothelioma; hence, plaintiffs' experts will generally testify that a history of any asbestos exposure in excess of background is sufficient to opine that asbestos caused plaintiff's mesothelioma.

In part because histories of exposure are subject to doubt and mesothelioma occurs without exposure to asbestos, defense experts look for histopathologic or radiologic evidence of asbestos exposure including the following:

(1) Asbestosis;

(2) Pleural plaques, especially bilateral;

(3) Asbestos bodies in the pathology slides; or

(4) Excessive fiber burden in the lungs.

Failing such evidence the mesothelioma is regarded as"spontaneous" or "idiopathic," i.e. without known cause.

Lung Cancer

Principally there are five types of lung cancer: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma, and adenosquamous carcinoma. All types of lung cancer occur in persons exposed to asbestos. Most types of lung cancer, particularly if diagnosed early, are subject to treatment with varying rates of remission. Unlike mesothelioma, lung cancer is not uniformly fatal within a short period of time.

The major confounding factor in the cause of lung cancer by asbestos is cigarette smoking. Obviously it is well known that cigarette smoking without exposure to asbestos can cause lung cancer. Most persons exposed to asbestos are also cigarette smokers. A debate presently rages regarding whether the risks of smoking and asbestos exposure are additive or multiplicative. One study shows that cigarette smoking increases the risk of

lung cancer eleven fold while asbestos exposure increases the risk of lung cancer approximately five fold when compared to the non-smoking, non-exposed population. The effects of both cigarette smoking and asbestos exposure were then found to be synergistic. As a result, the risk of lung cancer in a person who both smokes and is exposed to asbestos was calculated as a fifty-five fold increase in risk. On the other hand, more recent studies have argued that the risks are merely additive with a much lesser total risk. For a rather intensive, scientific explanation suggesting that the risk is less than multiplicative but more than additive, see Liddell FD. Joint Action of Smoking and Asbestos Exposure on Lung Cancer. Occupational and Environmental Medicine 59:495-496 (2002).

The question then arises how to determine whether or not asbestos exposure substantially contributed to cause a person's lung cancer when that person is also a long term cigarette smoker. Doctors testifying for plaintiffs generally testify that lung cancer is due to asbestos exposure if a particular plaintiff merely had evidence of asbestos exposure. On the other hand doctors testifying for the defense generally opine that mere evidence of asbestos exposure is insufficient; instead, they testify that findings of asbestosis, including evidence on x-rays or CT scans, must be found in the lungs before they will relate the plaintiff's lung cancer to his asbestos exposure. Some experts have taken a somewhat intermediate position, to-wit: lung cancer is attributable to asbestos exposure only when plaintiff or decedent has suffered exposure at a level that is equivalent to what should cause asbestosis.

Based upon research of a cohort of asbestos-cement workers, Dr. Murray Finkelstein has opined recently that the risk of lung cancer increases at doses below which asbestosis will not occur. See "Absence of Radiographic Asbestosis and the Risk of Lung Cancer Among Asbestos-Cement Workers: Extended Follow-up of a Cohort" American Journal of Industrial Medicine 53:1065 (2010).

Other Cancers

Plaintiffs claim that asbestos exposure causes a number of other cancers, such as laryngeal cancer, esophageal cancer, and colon cancer. This is not an exhaustive list. The causation of these cancers by asbestos is a hotly contested issue in the medical literature. The medical literature suggesting causation of these cancers by asbestos exposure is not nearly as persuasive (and in many instances very weak) as the literature relating to mesothelioma and lung cancer. As an example the famous Selikoff insulator studies do not control for other risk factors. In fact, the balance of medical literature on other types of cancer likely finds that asbestos exposure has not been proven to be the cause of these other types of cancer. However, there are notable exceptions. For example, Victor Roggli in the most recent edition of his book, The Pathology of Asbestos Associated Diseases, argues that high exposure to asbestos can cause laryngeal cancer.

Clearly there are problems associating these types of cancer with asbestos exposure of a particular plaintiff. Experts usually testifying for plaintiffs only require that there was exposure to asbestos in excess of background levels. However, such opinions ignore that these other types of cancer are more often caused by other factors. For example, diet, smoking, genetics, and the occurrence of colon polyps are the most important factors in causing colon cancer. In fact, oncology treatises often cite such factors as causing colon cancer without any mention of asbestos exposure.

Asbestosis

Asbestosis is a scarring of the lungs which creates interstitial fibrosis. Asbestosis seen today is usually relatively mild. However, asbestosis when it is sufficiently severe can be fatal. The person literally dies of suffocation due to the fibrous growth in the lungs. There are a number of causes of interstitial fibrosis of the lungs. For instance, chronic bronchitis in cigarette smokers can cause inflammation which leads to interstitial fibrosis. However, only asbestos exposure causes asbestosis.

Many plaintiffs' doctors have diagnosed asbestosis almost exclusively on the basis of x-rays or CT scans. The pulmonologist or radiologist who examines the x-rays

looks for characteristic interstitial markings on the x-rays, usually in the lower portions of both lungs in order to diagnose asbestosis. The severity of the asbestosis as seen on x-rays is rated on the ILO (International Labor Organization) scale. Persons in the United States who have been trained by NIOSH to read x-rays and rate them according to this scale are called "B-readers." The ILO provide two ratings for small irregular opacities that are consistent with but not necessarily diagnostic of asbestosis:

- Size of the opacities: s (up to 1.5 mm), t (1.5 to 3 mm), and r (3-10 mm)
- Profusion, i.e. extent of the opacities: rated 0-3. Profusion is rated by two numbers, e.g. 1/0. The first number is what the B reader most likely believes is the appropriate profusion rating while the second number, if different from the first, represents that the B reader is in some doubt about the proper reading and tells what he thinks would be the rating if the first number does not accurately represent the patient's condition.

CT scans are a more accurate aid in the diagnosis of asbestosis than x-rays but the ILO scale does not apply the review of CT scans. Radiology without more cannot reveal the cause of the fibrosis.

Plaintiffs may also have pulmonary function testing in support of a finding of asbestosis on their x-rays or CT scans. Such pulmonary function testing may reveal an impairment of the persons lung function. Some persons with clear signs of asbestosis in their lungs will still be asymptomatic and have no indications of significant impairment on pulmonary function testing. Other persons may have fairly mild asbestosis showing on x-rays yet have fairly extensive impairments on pulmonary function testing. The following explains a basic understanding of how to read PFT results:

Restrictive respiratory defect (consistent with asbestosis)

FEV1/FVC=normal or higher (above 65%)
AND
FVC=low (generally below 80% of predicted)

Obstructive respiratory defect (consistent with COPD from smoking)

FEV1/FVC=low (generally below 65%)

OR
Generally material improvement
with use of bronchodilators

FVC (forced vital capacity) = maximal volume of air exhaled with maximally forced effort from a position of maximal inspiration.
FEV1 (forced expiratory volume in one second) = the volume of air exhaled in the first second of time during the performance of FVC.
Pulmonary function testing in and of itself does not reveal the cause of the impairment.

There is variability in the reading of x-rays and CT scans to determine the presence of asbestosis. Plaintiffs and defendants' experts often disagree on whether the x-ray shows findings of asbestosis. Even without the influence of litigation there is variability in reading x-rays to determine the presence of asbestosis.

Many defense experts require four factors for a finding of asbestosis:

(1) The appropriate ILO rating upon reading an x-ray or CT scan;

(2) Impairment on pulmonary function testing;

(3) The presence of rales, i.e., characteristic lung sounds during breathing; and

(4) Evidence of exposure at a relatively significant level, well above background levels.

Plaintiffs experts will often diagnose asbestosis with a finding of pulmonary fibrosis and a history of asbestos exposure.

The weight of the medical literature indicates that asbestosis occurs only in the presence of relatively substantial exposure, i.e. 25 f/cc-years. For example, mesothelioma will occur in persons who have been exposed but do not exhibit any sign

of asbestosis. Asbestosis is not treatable and can be progressive even after exposure ceases. Studies have shown that a person with asbestosis has an increased risk of lung cancer.

Fortunately asbestos litigation does not present many serious cases of asbestosis at this time. The substantial exposures which caused asbestosis, principally in the asbestos factories and textile mills, have long since ceased. Practices which heavily exposed insulators to asbestos exposure have also ceased. However, there are occasionally exceptional cases.

Pleural Thickening/Plaques

Asbestos fibers as they reach the pleura of the lungs will cause an inflammatory reaction which leads to thickening of the pleura. Thickening of the pleura can become more pronounced and restricted to particular areas constituting a plaque. As the disease process progresses the plaque may become calcified. Pleural inflammation, thickening and even plaques can occur for some reasons unrelated to asbestos exposure. For example, the disease pleurisy may lead to these conditions. However, thickening or plaques on the lower portion of both lungs can be an indication of asbestos exposure.

Pleural thickening and plaques are normally asymptomatic appearing only on the patient's x-rays or CT scan. However, plaintiffs will contend that at least in some exceptional cases pleural thickening (or even plaques) can become sufficiently severe to restrict the activity of the lung. Such problems with the lung would be evident then on pulmonary function testing. When a plaintiff has impairment on pulmonary function testing but only has pleural thickening or plaques, the impairment may be due either to causes unrelated to asbestos exposure or an underlying asbestosis.

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