ASBESTOS-INDUCED LUNG AND PLEURAL DISEASE

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INTRODUCTION

My name is Samuel P. Hammar, M.D. I am board certified in anatomic and clinical pathology. I am the Director of Diagnostic Specialties Laboratory in Bremerton, Washington and am a Clinical Professor of Pathology and Environmental Sciences at the University of Washington Medical Center. I am a member of the US-Canadian Mesothelioma Panel and a member of the International Mesothelioma Panel. I am co-editor of two books, one titled *Pulmonary Pathology*, a 1,650 page textbook concerning the pathology of the lungs and chest cavity, and the other titled *Pulmonary Pathology Tumors* which discusses the various neoplasms of the lung and chest cavity. In the book I am a co-editor of titled *Pulmonary Pathology,* I was co-author of Chapter 28 titled *Asbestos* (the other co-author was Dr. Ronald F. Dodson, Chairman of Cell Biology and Environmental Sciences at the University of Texas at Tyler). I am the author of Chapter 32 of the book titled *Pulmonary Pathology* dealing with common lung neoplasms and the author of Chapter 34 which deals with pleural diseases, 90% of which discusses the entity mesothelioma. I have written numerous chapters in other books concerning mesothelioma and asbestos-induced diseases. I have published approximately 30 articles in peer-reviewed journals on asbestos-related lung diseases.

I am a co-editor of a book that is going to be published in year 2005 titled *Asbestos: Risk Assessment, Epidemiology and Health Effects.* The other co-editor of this book is Dr. Ronald F. Dodson, with whom I do research. I am a co-author of a book to be published by the International Mesothelioma Panel titled *Pathology of Malignant Mesothelioma.*

As a pathologist in Bremerton, Washington, I evaluate asbestos-induced lung disease on a regular basis since Bremerton is the home of the Puget Sound Naval Shipyard and is a small city in which a significant percentage of the population has been exposed to asbestos. As a pathologist, I see approximately 10-20 new mesothelioma cases per year in Bremerton, 20-30 new cases of asbestos-induced lung disease (pleural and/or parenchymal) per year and approximately 20 cases of primary lung cancer per year related to asbestos.

I was Chairman of the Pathology Section of the Lung Cancer Study Group that was in existence from 1977 to 1989. The main objective of the study group was to determine new and better ways to treat lung cancer and mesothelioma. My job was to make certain the diagnosis of each individual case was correct and that the tumor in each individual case was properly anatomically staged. I was the pathologist for the CARET study (carotene and retinoid acid efficacy trial) concerning whether anti-oxidant vitamins prevented or reduced the incidence of lung cancer and/or mesothelioma in individuals who were exposed to asbestos and/or cigarette smoke. I was a member of the WHO Committee that wrote a book published in 1999 on the current classification of lung cancer and mesothelioma. I was a contributor to a book recently published by the IARC Press titled *Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart.*

I was consulted by Mr. Nathan Finch, counsel to the Owens Corning Asbestos Claimants Committee, to provide general information concerning asbestos and information on asbestos-induced diseases for the Owens-Corning hearing. A copy of my curriculum vitae is attached to my expert report, as is a copy of the trials and depositions I have participated in between 2000 and 2004.

My hourly rate for reviewing this material is $500.00 per hour.

INFORMATION ABOUT ASBESTOS

Asbestos is a naturally occurring fibrous mineral with unique properties that has resulted in it being used in numerous products. Asbestos is a lightweight, thermally and/or chemically resistant material with high tensile strength that, because of these qualities, has been extensively used in over 3,000 different products. Asbestos has extensively been used as a fire retardant and insulating material. A relatively brief history of asbestos has recently been published by Abratt, et al. (Abratt RP, Vorobiof DA, White N. *Asbestos and mesothelioma in South Africa.* Lung Cancer 2004;45S:S3-S6). As early as 4000 BCE (before Christian era), asbestos was used for wicks in lamps and candles. "Asbestos" means inextinguishable or unquenchable. From 2000-3000 BCE, embalmed bodies of Egyptian pharaohs were wrapped in asbestos clothes to offset the ravages of time. In 2500 BCE, asbestos was used in Finland to strengthen clay pots. From 800-900 AD, there was anecdotal evidence that Charlemagne's table cloth was made from woven asbestos. During 1000 AD, Mediterranean people used chrysotile from Cyprus and tremolite from upper Italy for the fabrication of cremation clothes, mats and wicks for temple lamps. During the period 1300-1400, Marco Polo visited an asbestos mine in China in the latter half of the 13th century and concluded that asbestos was a stone. He laid to rest the myth that asbestos was the hair of a woolly lizard. During the early 1700s, asbestos papers and boards were made in Italy. In 1724 Benjamin Franklin brought a purse made of asbestos to England. The purse is now in the Natural History Museum. In 1828 a U.S. patent was issued for asbestos insulating material to be used in steam engines. In 1853 asbestos helmets and jackets were worn by the Parisian Fire Brigade. In 1866 molded lagging material was made from water, glass and asbestos. In 1896 the first asbestos brake linings were made by Ferodo Ltd., in England. In 1900 high pressure asbestos gaskets were made by Klinger in Austria. In 1913 asbestos pipes were first developed in Italy. In 1919 standard corrugated sheet asbestos was introduced in Australia by Hardies. From 1939 to 1945, wartime use included fireproof suits and parachute flares. In 1939 in the film "The Wizard of Oz," the Wicked Witch of the West appeared on a broom made of asbestos. From 1945 to 1975, post-war construction projects relied heavily on the use of asbestos, reaching an all-time high in 1973. During the 1990s, the solid fuel boosters of the space shuttle were insulated with asbestos, one of the few remaining current uses.

Widespread use of asbestos-containing materials resulted in exposures of millions of individuals who were then at risk for developing asbestos-related diseases. Asbestos-related diseases typically have a long latency period (time from first exposure to diagnosis of disease). Asbestos has been shown to produce two basic disease processes: cancer and scarring processing.

Cancer diseases caused by asbestos include lung cancer, mesothelioma and other cancers such as cancers of the digestive tract and kidney. The scarring diseases include the disease asbestosis (scarring of the supportive framework of the lung), visceral pleural fibrosis, hyaline pleural plaque, round atelectasis and fibrothorax. Asbestos can also cause a pleural effusion many years after a person was last exposed to asbestos.

Asbestos is sometimes stated to be ubiquitous in our environment and that all individuals are exposed to asbestos every day. This is incorrect. The majority of individuals under age 30 have not been exposed to asbestos and will not be exposed to asbestos except under rare circumstances. At this time, the majority of air samples analyzed from the general environment do not contain asbestos. In cities where air fiber analysis has been done, levels of asbestos have been in the range of 0.0005-0.00005 fibers per cubic centimeter. Numbers of asbestos fibers in buildings vary depending on the age of the building, what materials were used to

insulate the building and how much disrepair the building was in (Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of asbestos-associated diseases.* Boston: Little, Brown & Company 1992:29-30). In 1999, Dodson, et al., evaluated tissue burden of asbestos in nonoccupationally exposed individuals from East Texas, a geographical location in which there was considerable use of asbestos. Three-fourths of the 33 individuals in East Texas had no asbestos bodies in their lung tissue and 1/3rd of the 33 individuals had no asbestos fibers in their lung tissue. This was age dependent, with younger individuals characteristically having no asbestos and older individuals having either a small amount of chrysotile asbestos or occasionally having amphibole asbestos (Dodson RF, Williams MG, Huang J, Bruce JR. *Tissue burden of asbestos in nonoccupationally exposed individuals from East Texas.* Am J Ind Med 1999;35:281-286).

The body has natural defense mechanisms to try to protect it from dusts like asbestos and other particulate matter. These defense mechanisms include the mucus and hairs in the nose; the epithelial lining of bronchi, which include ciliated cells and mucus secreting cells that are part of the system referred to as the "mucociliary escalator apparatus" that clears particulates from the lining of the air tubes; and the alveolar macrophages that engulf particulate matter up to a size of about 5 µm. in greatest dimension. Despite these clearance mechanisms, occupationally exposed individuals can have over 60 million asbestos fibers per gram of dry lung tissue and over 1 million asbestos bodies per gram of dry lung tissue (Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP. *Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.* Ultrastruct Pathol 1997;21:321-336).

Asbestos is cleared from the lung over time and perhaps that explains some observations in the 1950s that as individuals became older, the number of asbestos bodies found in their lung tissue seemed to decrease. Chrysotile fibers are thought to be more readily cleared from the lung than amphibole fibers. Chrysotile has a half-life in the lung of approximately 90-120 days. (A) Churg A, Green FHY. *Occupational Lung Disease.* In: Thurbeck WM, Churg AM, eds., Pathology of the lung, 2nd Ed. New York: Thieme, 1995:851-929; (B) Roggli VL, Brody AR. *Experimental models of asbestos-related diseases.* In: Roggli VL, Greenberg SD, Pratt PC, eds., Pathology of asbestos-associated diseases. Boston: Little, Brown & Co. 1992:257-297; (C) Churg A. *Nonneoplastic diseases caused by asbestos.* In: Churg A, Green FHY, eds., Pathology of occupational lung disease. New York: Igaku-Shoin, 1988:213.277; (D) Jones DH, Vincent JH, Addison J, et al. *The fate and effect of inhaled chrysotile asbestos fibers.* Ann Occup Hyg 1994;38, suppl 1:619-629. Clearance of short fibers is significantly greater than clearance of longer fibers. Amphiboles are cleared from lung and have a half-life in lung tissue of about 20 years for amosite and approximately 5-10 years for crocidolite. (A) Churg A, Vedal S. *Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure.* Am J Respir Crit Care Med 1994;150:663-669; (B) Berry G, Rogers AJ, Pooly RD. *Mesotheliomas – asbestos exposure and lung burden.* IARC 1989;90:486-496; (C) Du Toit RS. *An estimate of the rate at which crocidolite asbestos fibers are cleared from the lung.* Ann Occup Hyg 1991;35:433-438; (D) de Klerk NH, Musk AW, Williams VM, et al., *Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoom Gorge, Western Australia.* Am J Ind Med 1996;30:579-587). de Klerk could find no difference between the clearance rates of long and short fibers and Oberdörster estimated human clearance half-lives to be about 90-100 days for chrysotile, 200-1500 days for crocidolite fibers >16 µm in length based on extrapolated rat and primate inhalation data (Oberdörster G. *Macrophage-associated responses to chrysotile.* Ann Occup Hyg 1994;38:601-615).

The concentration of asbestos found in the lung tissue of individuals in the general population without occupational or bystander exposure to asbestos is age dependent, but certain levels

have been found. For example, the upper limits of normal reported by Churg and Warnock were 100 asbestos bodies per gram of wet lung tissue, whereas Roggli, Dodson and Hammar reported 20 asbestos bodies per gram of wet lung tissue as the upper limits of normal in most adults (Hammar SP, Dodson RF. *Asbestos.* Chapter 28. In: Dail DH, Hammar SP, eds., Pulmonary Pathology, 2nd Ed. New York: Springer-Verlag, 1994:901-983). In Western Washington, about 50% of women whose lung tissue has been analyzed by digestion analysis have no asbestos bodies, whereas most men have asbestos bodies (personal observation). In our evaluation of mesothelioma patients' lung tissue, there is considerable variation in the concentration of asbestos found in individuals with the same disease (Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP. *Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.* Ultrastruct Pathol 1997;21:321-336). What is not known at this point in time is how much asbestos it actually takes to produce a given disease. Published data suggests it requires higher concentrations of asbestos to cause lung cancer and asbestosis than it does to cause mesothelioma and pleural plaques (*Asbestos, asbestosis and cancer: the Helsinki criteria for diagnosis and attribution.* Scand J Work Environ Health 1997;23:311-316).

The mechanism by which asbestos causes disease is not totally understood, although a significant amount of information has been recorded. As reviewed by Kamp and Weitzman, asbestos can injure by direct interaction with the cells or can cause certain types of chemical reactions to occur such as the development of oxygen and nitrogen free radicals that can cause injury (Kamp DW, Weitzman SA. *The molecular basis of asbestos induced lung injury.* Thorax 1999 Jul;54(7):638-52). Of interest, it appears that for every adverse reaction that asbestos causes in the human body, there is an opposite reaction that tries to repair that injury. Why some individuals develop an asbestos-related disease and others do not when both are exposed to the same amount of asbestos is unknown, although this is thought to be due to individual susceptibility and is probably genetically related, although exact mechanisms are not well understood. There has been published evidence that glutathione S-transferase activity is inversely correlated with the development of lung cancer and asbestosis. (A) Abidi P, Afaq F, Arif JM, et al. *Chrysotile-mediated imbalance in the glutathione redox system in the development of pulmonary injury.* Toxicol Lett. 1999; May 20;106(1):31-9; (B) Kelsey KT, Nelson HH, Wiencke JK, et al. *The glutathione S-transferase theta and mu deletion polymorphisms in asbestosis.* Am J Ind Med 1997 Mar;31(3):274-9; (C) Hirvonen A, Saarikoski ST, Linnainmaa K, et al. *Glutathione S-transferase and N-acetyltransferase genotypes and asbestos-associated pulmonary disorders.* J Natl Cancer Inst 1996 Dec 18;88(24):1853-6; (D) Anttila S, Luostarinen L, Hirvonen A, et al. *Pulmonary expression of glutathione S-transferase M3 in lung cancer patients: association with GSTM1 polymorphism, smoking and asbestos exposure.* Cancer Res 1995 Aug 1;55(15):3305-9; (E) Smith CM, Kelsey KT, Wiencke JK, et al. *Inherited glutathione-S-transferase deficiency is a risk factor for pulmonary asbestosis.* Cancer Epidemiol Biomarkers Prev 1994 Sep;3(6):471-7.

All asbestos-related diseases are dose-response related and it has generally been observed that the longer one has been exposed to asbestos and the greater the concentration of asbestos is in an individual's body, the greater risk that individual has for developing an asbestos-related disease. What can't be determined at the present time is which person who has been exposed to asbestos will eventually develop an asbestos-related disease. In any given disease, there is always a range of concentration of asbestos that one finds in the lung or pleural tissue of such individuals.

MESOTHELIOMA

Mesotheliomas are malignant tumors that arise from the lining of the body cavities. During embryogenesis, a single body cavity called the celomic cavity is divided into the pleural (chest), peritoneal (abdominal) and pericardial (heart) cavities (Hammar SP. *Pleural diseases.* Chapter 34. In: Dail DH, Hammar SP. eds., 2nd Ed. Pulmonary Pathology. New York: Springer-Verlag, 1994:1463-1579). These cavities are lined by a thin, almost invisible membrane similar in appearance to Saran wrap made up of an outer mesothelial layer and underlying connective tissue component the entire thickness of about 0.4 mm. Mesotheliomas are neoplasms derived from the cells that form this membrane. Mesotheliomas begin as small nodules that originate from these membranes and, over time, coalesce to form a rind that encases the organ(s) within the respective body cavity. Approximately 90-95% of mesotheliomas develop in the chest cavity and are called pleural mesothelioma. Five to 10% develop in the abdominal cavity and are called peritoneal mesothelioma. Rare mesotheliomas arise from the pericardium and from tunica vaginalis, the latter being an invagination of the peritoneum. Benign mesothelial nodules called adenomatoid tumors occur in epididymis, uterus and rarely the pleura. Adenomatoid tumors can be mistaken for malignant mesothelioma.

Mesotheliomas are divided into four histologic tissue types based on what the cancer cells look like when viewed through a light microscope: 1) epithelial mesothelioma; 2) sarcomatoid (fibrous) mesothelioma; 3) biphasic mesothelioma; and 4) desmoplastic mesothelioma. Mesotheliomas show a marked variability in how they look microscopically that can cause difficulty in accurately diagnosing them.

The only epidemiologically established cause of mesothelioma is asbestos. Approximately 90% of mesotheliomas in men are caused by asbestos and, in our experience, 70% of mesotheliomas in women are caused by asbestos (Hammar SP, Roggli VL, Oury TD. *Malignant mesothelioma in women.* Lung Cancer 1977;18, suppl 1:236). Most women who develop mesothelioma thought to be caused by asbestos had domestic bystander exposure to asbestos. Dodson, et al., (Dodson RF, O'Sullivan M, Brooks DK. Hammar SP. *Quantitative analysis of asbestos burden in women with mesothelioma.* Am J Ind Med 2003;43:188-195) reported 16 cases of mesothelioma in women whose lung tissue was evaluated for asbestos fiber concentration by digestion analysis. Several women with domestic bystander exposure to asbestos had slightly elevated concentrations of asbestos in their lung tissue. In addition, Dawson, et al., (Dawson A, Gibbs AR, Pooley FD, Griffiths SM, Hoy J. *Malignant mesothelioma in women.* Thorax 1993;48:269-274) reported that approximately 80% of mesothelioma in women were related to asbestos. In four women who stated they were not exposed to asbestos, over 2 million asbestos fibers per gram of dry lung tissue were identified by asbestos digestion analysis, thus suggesting that individuals may not know how they were exposed to asbestos.

Other causes of mesothelioma have been reported, although are rare. Most non-asbestos causes of mesothelioma were reported by Peterson, et al., (Peterson JT Jr, Greenberg SD, Buffler PA. *Non-asbestos-related malignant mesothelioma: a review.* Cancer 1984;54:951-960). Potentially, malignant mesothelioma can develop at the site of serosal injury caused by any agent. Most causes cited by Peterson, et al., have not withstood the test of time. At this point in time, therapeutic radiation given to treat other tumors is thought to be causative of mesothelioma, as are some cases of chronic injury to the serosal lining of body cavities. One recent issue that has arisen concerning mesothelioma causation concerns SV40 virus. As most recently reported in Nature Reviews, Cancer in December 2002, there is no proof at this time that SV40 virus causes mesothelioma, although investigation is ongoing (Gazdar AF, Butel JS, Carbone M.

SV40 and human tumours: myth, association or causality? Nat Rev Cancer 2002 Dec;2:957-64). Erionite, a fibrous zeolite, has been reported to cause mesothelioma in individuals in Central Turkey who use erionite in various construction activities. A recent report stated all cases of mesothelioma caused by erionite occurred only in individuals who were related to each other (Emri S, Demir AU. *Malignant pleural mesothelioma in Turkey, 2000-2002.* Lung Cancer 2004 Aug;45 Suppl 1:S17-20).

With respect to mesothelioma causation by asbestos, it is generally accepted that amphibole asbestos is more tumorigenic in causing mesothelioma than chrysotile asbestos on a fiber-for-fiber basis (Hammar SP. *Pleural diseases.* Chapter 34. In: Dail DH, Hammar SP, eds., 2nd Ed. Pulmonary Pathology. New York: Springer-Verlag, 1994:1463-1579). The reported ratio of the variability in tumorigenicity is great. Hodgson & Darnton suggested the tumorigenicity of asbestos fibers on a fiber-for-fiber basis was 500-100-1 for crocidolite-amosite-chrysotile, respectively (Hodgson JT, Darnton A. *The quantitative risk of mesothelioma and lung cancer in relation to asbestos exposure.* Ann Occup Hyg 2000 Dec;44(8):565-601). In contrast, Dr. William Nicholson concluded crocidolite was about 10-12 times more potent than chrysotile in causing mesothelioma and that chrysotile and amosite were approximately equal (Nicholson WJ. *Comparative dose-response relationship of asbestos fiber types: magnitude and uncertainties.* Ann NY Acad Sci 1991 Dec;643:74-84). Smith and Wright, however, observed that the ten cohorts with the largest number of mesothelioma cases occurred in those in which the dominant exposure to asbestos was chrysotile (Smith AH, Wright CC. *Chrysotile asbestos is the main cause of pleural mesothelioma.* Am J Ind Med 1996 Sept;30(3):252-266). The article by Drs. Smith and Wright also argues that the relative dose of asbestos plays just as important a role in causing mesothelioma as the relative potency of a given fiber type.

A relatively recent experimental study looking at the development of mesotheliomas in rats after direct intraperitoneal injection with asbestos and other substances found there were an approximate equal number of mesotheliomas in the rats directly injected with amosite, crocidolite and UICC-chrysotile B, which is a mixture of chrysotile from nine different Quebec chrysotile mines. The vehicle used to inject the asbestos and a non-asbestos substance called wollastonite did not cause mesothelioma (Rittinghausen S, Ernst H, Muhle H, Mohr U. *Atypical malignant mesotheliomas with osseous and cartilaginous differentiation after intraperitoneal injection of various types of mineral fibres in rats.* Exp Toxic Pathol 1992;44:55-58).

Another issue concerning mesothelioma causation is whether the asbestos found in the lung or that translocated to the pleura is most important in causing mesothelioma. The carcinogenic (tumorigenic) agent responsible for causing a malignant neoplasm is thought to have to be in the immediate vicinity of where the tumor is located to be considered causative. Suzuki and Yuen discussed asbestos fiber types in the pleura and mesothelioma tumor tissue. They found the dominant fiber in pleural plaque and in tumor tissue to be chrysotile. This information suggests chrysotile is the most important factor in mesothelioma tumorigenesis (Suzuki Y, Yuen SR. *Asbestos fibers contributing to induction of human malignant mesothelioma.* Ann NY Acad Sci 2002; 982:160-176). However, Boutin, et al. suggests most pleural mesotheliomas arise in black spots on the parietal pleura where amphibole asbestos is concentrated (Boutin C, Dumortier P, Rey F, et al. *Black spots concentrate oncogenic asbestos fibers in the parietal pleura: thoracoscopic and mineralogic study.* Am J Respir Care Med 1996 Jan;153(1):444-449).

As reported by us in 1997, most patients have more than one type of asbestos in their lung tissue (Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP. *Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.* Ultrastruct Path 1997;21:321-336). Amosite

asbestos is the dominant fiber type found in the lungs of mesothelioma patients in the United States. Approximately 50% of patients have chrysotile in their lungs and the other 50% probably had chrysotile in their lungs but it was not identified due to clearance.

LUNG CANCER

Lung cancer is the second major disease identified to be caused by asbestos. Lung cancer associated with asbestos was first described in 1936 by Lynch and Smith (Lynch KM, Smith WA. Pulmonary asbestosis. III. *Carcinoma of the lung in asbestosis.* Am J Cancer 1936;14:56-64). Wedler found a high incidence of lung cancer among individuals in Europe who had been diagnosed with asbestosis (Wedler HD. Uber den Lungenkrebs bei Asbestose. Deut Med Woch 1943;69:575-576). Merewether also found an increased incidence of lung cancer and neoplasms referred to as "tumors of the pleura" (? mesothelioma) in asbestos factory workers compared to the non-asbestos exposed population (Merewether ERA. Annual report of the chief inspector of factories for the year 1947. London: His Majesty's Stationery Office 1949:78-81).

There are four issues that currently concern lung cancer and attribution to asbestos: 1) are there histologic types and specific locations of lung cancers that are more closely associated with asbestos exposure?; 2) what is the concentration of asbestos it takes to cause lung cancer and is there a threshold below which lung cancer will not occur at an increased incidence?; 3) is it necessary to have the disease asbestosis in an individual before lung cancer causation can be attributed to asbestos?; and 4) what is the relationship or interaction between asbestos and cigarette smoke carcinogens in causing lung cancer (synergism)?

All four major histological types of lung cancer (adenocarcinoma, squamous carcinoma, small cell lung cancer and large cell undifferentiated carcinoma) are observed in persons exposed to asbestos occurring at a rate similar to those in non-asbestos exposed individuals. The anatomic location of the neoplasm (upper lobe vs. lower lobe; peripheral vs. central) is not significant in determining whether a primary lung cancer is caused by asbestos. The issues of concentration of asbestos necessary to cause lung cancer and whether asbestosis is necessary to attribute lung caner causation to asbestos have been hotly debated. These issues have been extensively discussed by Henderson, et al. (Henderson DW, de Klerk NH, Hammar SP, et al. *Asbestos and lung cancer: is it attributable to asbestosis or to asbestos fiber burden?* Chapter 6. In: Corrin B, ed., Pathology of Lung Tumors. New York: Churchill-Livingstone, 1997:83-118). Three potential hypotheses were discussed: H1 – does asbestos modify lung structure so that fibrotic lung parenchyma becomes more prone to neoplastic transformation by carcinogens in tobacco smoke perhaps mediated by adjuvant effects of cytokines?; H2 – is the risk of lung cancer increased only when the inhaled fiber burden falls into the range recorded for asbestosis?; and H3 – does any inhaled dose of asbestos have the potential to increase the risk of lung cancer? This author believes that inhaled dose is the most important factor in attributing lung cancer to asbestos exposure.

Exactly how much asbestos it takes to cause lung cancer is difficult to state. In 1986, Warnock and Isenberg (Warnock ML, Isenberg W. *Asbestos burden and the pathology of lung cancer.* Chest 1986 Jan;89(1):20-26) evaluated 75 men with primary lung cancer, most of whom had been exposed to asbestos. They found cases of individuals with pathologic asbestosis whose lung tissue contained as little as 100,000 asbestos fibers per gram of dry lung and suggested that if those men's lung cancer were related to asbestos, then those men's lung cancer whose lung tissue contained at least 100,000 asbestos fibers per gram of dry lung should also be causally related to asbestos.

Others have stated that a cumulative exposure of 25 fiber/cc years is estimated to increase the risk of lung cancer 2-fold, as is one year of heavy asbestos exposure or 5-10 years of moderate exposure. Finnish investigators have reported a 2-fold increase in lung cancer is related to a fiber level of 2 million fibers greater than 5 μm long per gram of dry lung tissue or 5 million fibers per gram of dry lung tissue greater than 1 μm long. This fiber concentration is stated to be approximately equivalent to 5,000-15,000 asbestos bodies per gram of dry lung tissue (500-1,500 asbestos bodies per gram of wet lung tissue).

Because chrysotile is cleared rapidly from the lung, tissue concentration values cannot be used to determine if lung cancer was caused by chrysotile. Fiber/cc/years is the best criterion for determining if chrysotile exposure was enough to cause lung cancer.

Henderson, et al., (*Pathology*: in press) reviewed literature between 1997 and the present concerning the issue of asbestos-induced lung cancer and pointed out a relative risk of less than 2 is indicative of a significant increase in lung cancer incidence and suggested that fiber year cumulative exposures less than 25 fiber cc years can be associated with a significant increase in lung cancer. They also discussed the issue of individual susceptibility (genetic susceptibility) that has the potential to cause an increased incidence of lung cancer at the same level of occupational exposure.

The issue of synergism suggests cigarette smoke carcinogens and asbestos cause an increased incidence of lung cancer together that is greater than that caused by either one alone. The most often quoted study was by Selikoff, et al., (Selikoff EJ, Hammond EC, Churg J. *Asbestos exposure, smoking and neoplasia.* JAMA 1968;204:104-110) where they found there was an approximately 5-fold increase in the incidence of lung cancer in asbestos-exposed persons compared to non-smoking, non-asbestos-exposed workers; an 11 times increase of lung in cigarette smokers not exposed to asbestos; and an approximately 61-fold increase in the incidence of lung cancers in persons who were cigarette smokers and occupationally exposed to asbestos.

The issue of synergism has been reviewed by Saracci who studied the interactions of tobacco smoking and other agents in the etiology of cancer. Saracci listed 13 studies evaluating this subject and came to the conclusion that in 10 of the 13 studies, there was evidence of multiplicative synergism between cigarette smoke and asbestos in causing lung cancer (Saracci R. *The interactions of tobacco smoking and other agents in cancer etiology.* Epidemiol Rev 1987;9:175-193). At this time, the only way that an individual can reduce their risk of developing lung cancer from asbestos is to stop smoking cigarettes.

OTHER CANCERS

With respect to other types of cancers caused by asbestos, it is this author's opinion that the ones associated with an asbestos etiology include laryngeal cancer, GI tract cancer and kidney cancer in individuals who are exposed to moderate to high amounts of asbestos (Greenberg SD, Roggli VL. *Other neoplasia.* Chapter 8. In: Roggli VL, Greenberg SD, Pratt PC. Pathology of asbestos-associated diseases. Boston: Little, Brown & Co., 1992:211-222). Three separate pathologic studies have shown an association between laryngeal cancer and parietal pleural plaques. The basis for attribution of non-pulmonary cancers to asbestos is based on the assumption that asbestos is translocated to the sites where these neoplasms occur. As reported by the Selikoff group, there is an increased relative risk of laryngeal cancer (relative risk 1.61-1.70), kidney cancer (relative risk 1.70-1.96) and GI tract cancers (relative risk 1.37-2.61).

With respect to lymphoma/myeloma/lymphocytic leukemia, there have been several case reports of these types of neoplasms associated with asbestos exposure. Asbestos translocates to lymph nodes and is reported to cause abnormalities in the immune system. An elevated number of lymphomas have been reported in persons exposed to asbestos as reviewed by Roggli and Greenberg (Greenberg SD, Roggli VL. *Other neoplasia.* Chapter 8. In: Roggli VL, Greenberg SD, Pratt PC, eds., Pathology of asbestos-associated diseases. Boston: Little, Brown & Co., 1992;211-222).

NON-NEOPLASTIC DISEASES CAUSED BY ASBESTOS

Non-neoplastic diseases caused by asbestos include asbestos-induced pleural effusion, visceral pleural fibrosis, parietal pleural fibrosis, hyaline pleural plaques, round atelectasis, fibrothorax, asbestosis, organizing pneumonia, granulomatous changes and hypersensitivity pneumonia changes. Pathologic and other information concerning these conditions are discussed in detail in Chapter 28 of Pulmonary Pathology (Hammar SP, Dodson RF. *Asbestos.* Chapter 28. In: Dail DH, Hammar SP, eds., 2nd Ed. Pulmonary Pathology. New York: Springer-Verlag, 1994;901-983).

Two recent publications have provided an update on issues related to nonmalignant asbestos diseases: 1) Cugell DW, Kamp DW. *Asbestos and the pleura: a review.* Chest 2004;125:1103-1117; and 2) Guidotti TL, Miler A, Christian D, et al. *Diagnosis and initial management of nonmalignant diseases related to asbestos.* Am J Resp Crit Care Med 2004;170:691-715).

In 1992, this author reviewed the controversies and inconsistencies in the diagnosis of asbestosis (Hammar SP. *Controversies and uncertainties concerning the pathologic features and pathologic diagnosis of asbestosis.* Semin Diag Pathol 1992;9(2):102-109). Controversies, inconsistencies and uncertainties continue to exist. Some of these are listed below:

1) Words "asbestos" and "asbestosis" are often used inappropriately. Asbestosis by definition is scarring of lung parenchymal tissue by asbestos.
2) The diagnosis of asbestos-induced pleural effusion is a diagnosis of exclusion. Why do asbestos-induced pleural effusions often occur many years after last exposure? What is it that causes these often bloody effusions to occur at a given time?
3) Do parietal pleural hyaline pleural plaques cause symptoms? Is a certain amount of involvement of the parietal pleura necessary to cause symptoms or an abnormality of pulmonary function?
4) Why aren't hyaline pleural plaques seen on the visceral pleura to the same extent they are seen in the parietal pleura?
5) What is the pathogenesis of hyaline pleural plaques?
6) In cases of round atelectasis, is it the asbestos found in the thickened visceral pleura that results in invagination of the visceral pleura?
7) Does round atelectasis cause symptoms?
8) Is the CAP-NIOSH grading scheme for asbestosis reproducible?
9) Is asbestosis uniform throughout the lung? Is it true that asbestosis begins in the lower lobes? Is it correct that asbestos fiber concentrations are about equal in the upper lobe vs. the lower lobes?
10) What is the mechanism by which asbestosis progresses in the absence of continued exposure to asbestos?

Respectfully submitted,

Sam Hammar