

ASBESTOS-INDUCED LUNG AND PLEURAL DISEASE

Samuel P. Hammar, M.D.

Evaluation for W.R. Grace Asbestos Claimants Committee
c/o Caplin & Drysdale, Chtd.

One Thomas Circle NW, Suite 1100

Washington DC 20005

Phone (202) 862-7801

Fax (202) 429 3301

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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 U.S.-Canadian Mesothelioma Panel and a member of the International Mesothelioma Panel.

I am the co-editor of *Pulmonary Pathology*, a 1,650 page textbook on the pathology of the lungs and chest cavity, and of *Pulmonary Pathology Tumors* which discusses the various neoplasms of the lung and chest cavity. I am co-author of Chapter 28 in *Pulmonary Pathology* titled *Asbestos* (the other co-author was Dr. Ronald F. Dodson, currently of ERI Analytical in Tyler, Texas, with whom I do research). I am the author of Chapter 32 in *Pulmonary Pathology* dealing with common lung neoplasms, and of Chapter 34 which deals with pleural diseases, 90% of which discusses the entity mesothelioma. The 3rd edition of Dail-Hammar *Pulmonary Pathology* is scheduled to be published in 2007. I am co-editor of the book titled *Asbestos: Risk Assessment, Epidemiology and Health Effects* published in 2006. The other co-editor was Dr. Ronald F. Dodson. I am co-author of a book published by the International Mesothelioma Panel titled *Pathology of Malignant Mesothelioma*. I have written numerous chapters in other books concerning mesothelioma and asbestos-induced diseases and have published approximately 40 articles in peer-reviewed journals on asbestos-related lung diseases.

I was the 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 retinoic 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*.

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 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 asked by Mr. Nathan Finch of Caplin & Drysdale, counsel to W.R. Grace Asbestos Personal Injury Claimants Committee, to provide general information concerning asbestos and information on asbestos-induced diseases for the W.R. Grace hearing.

A copy of my curriculum vitae is attached to my expert report, as is a copy of the trials and depositions in which I have participated between 2002 and 2006. My hourly consultation rate 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 products. Asbestos has extensively been used as a fire retardant and insulating material. A relatively brief history of asbestos was 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 tablecloth 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. Brake linings continue to contain asbestos, usually chrysotile asbestos, and pose a health risk to workers and their families (Lemen RA. *Asbestos in brakes: exposure and risk of disease*. Am J Ind Med 2004;45:229-237; and Egilman DS, Billings MA. *Abuse of epidemiology: Automobile manufacturers manufacture a defense to asbestos liability*. Int J Occup Environ Health 2005;11:360-371).

Gee and Greenberg published an excellent review of asbestos and its adverse effects on health and the delay in recognizing the adverse effects on health (Gee D, Greenberg M. *Asbestos: from 'magic' to malevolent mineral*. In: Late lessons from early warnings: the precautionary principle 1896-2000). A summary of the lessons of the asbestos story is provided in their chapter on pages 59 through 61 (see section 5.7 in their chapter). Included in their chapter is France's ban on all types of asbestos (Table 5.1 from their chapter).

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.

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 and can cause unusual and localized diseases in the lung.

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 (In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of asbestos-associated disease*. 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 mucous 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, which might explain observations in the 1950s that as individuals became older, the number of asbestos bodies found in their lung tissue decreases. 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, Vedral 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, Pooley 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). However, 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 and 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. 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 cause injury 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; and Atkinson MAL. *Molecular and cellular responses to asbestos exposure. In: Dodson RF, Hammar SP, eds. Asbestos: Risk assessment, epidemiology, and health effects. Boca Raton, CRC, Taylor-Francis, 2006:91-136*). 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.

Studies are now underway to determine if serum markers for osteopontin (Cullen MR. *Serum osteopontin levels—is it time to screen asbestos-exposed workers for pleural mesothelioma?* N Engl J Med 2005;353:1564-73) and soluble mesothelin-related peptides are useful in the early detection of mesothelioma (Robinson BW, Creaney J, Lake R, et al. *Mesothelin-family proteins and diagnosis of mesothelioma.* Lancet 2003;362:1612-6).

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.

Because one cannot tell which exposures caused a mesothelioma or lung cancer, one cannot state that one exposure to asbestos caused the disease and another exposure did not. All exposures to all types of asbestos fibers act in concert to produce disease; it is the cumulative exposure to asbestos fibers that cause the disease.

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; and Galateau-Salle F. Pathology of malignant mesothelioma. Springer-Verlag, 2006). These cavities are lined by a thin, almost invisible membrane similar in appearance to thin plastic wrap made up of an outer mesothelial layer and underlying connective tissue component, the entire thickness being approximately 0.4 mm. Mesotheliomas are neoplasms derived from the cells that form this membrane. Mesotheliomas begin as small nodules that originate from cells that form 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.

Leigh et al. (Leigh J, Davidson P, Hendrie L, Berry D. *Malignant mesothelioma in Australia, 1945-2000*. Am J Ind Med 2002;41:188-201) stated that when earlier cases of mesothelioma that were classified as "no history of exposure" were reviewed, it was found that 57 of the 203 so classified cases had a history of asbestos exposure recorded. Thus, only 19% had no known history. Leigh and colleagues stated that of the "no known history" group, 81% had fiber counts greater than 200,000 fibers/gram dry lung and 30% had more than 10⁶ fibers per gram of dry lung greater than 2 µm long, including some fibers longer than 10 µm. The authors pointed out that dust exposure is not always recognized as such and it was more likely to be seen in cases of women than men. It was also pointed out that even in the absence of asbestos fibers

in the lung, it did not negate the possibility that asbestos fibers could have initiated mesothelioma and then be cleared to another site.

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). The most recent articles on the potential for SV40 virus to cause mesothelioma have suggested there is no association between SV40 virus and the development of mesothelioma (Manfredi JJ, Dong J, Liu W, et al. *Evidence against a role for SV40 in human mesothelioma. Cancer Res* 2005;65:2602-2609; and Lopez-Rios F, Illei PB, Rusch V, Ladanyi M. *Evidence against a role for SV40 infection in human mesotheliomas and high risk of false-positive PCR results owing to presence of SV40 sequences in common laboratory plasmids. Lancet* 2004;364:115-1166). 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; and Dogan AU, Baris YI, Dogan M, Emri S, Steele I, Elmishad AG, Carbone M. *Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey. Cancer Res* 2006;66:5063-5068).

The World Health Organization's recently drafted policy paper titled "Elimination of Asbestos-related Diseases" pointed out that all types of asbestos are capable of causing asbestosis, lung cancer, mesothelioma and other cancers. The general consensus at this point in time is there is no minimal threshold dose of inhaled asbestos below which there is no increased risk of mesothelioma. A 2000 review article on the quantitative risks of mesothelioma related to asbestos exposure by Hodgson and Darnton adopted a "no threshold" approach. As set forth in Table 11 in their review on dose-response relationships between asbestos and mesothelioma, Hodgson and Darnton estimated that a cumulative exposure of 1 fiber/mL-year for crocidolite yields a lifetime risk "best" estimate of about 650 mesothelioma deaths/100,000 (range = 250-1500), 90/100,000 for amosite (range = 15-300), and 5/100,000 for chrysotile (range = 1-20). For a cumulative exposure of 0.1 fibers/mL-years, these authors set forth a "best" estimate of about 100 deaths per 100,000 exposed for crocidolite with a highest arguable estimate of 350 and a lowest of 25; for amosite, the corresponding figures were 15 deaths per 100,000 with a highest arguable estimate of 80 and a lowest of 2; at this level of exposure, the risk for chrysotile was "probably insignificant," with a highest arguable estimate of 4 deaths per 100,000. For a cumulative exposure of 0.01 fibers/mL-years, the "best" estimate was about 20 deaths per 100,000 exposed for crocidolite with a highest arguable estimate of 100 and a lowest of 2; for amosite, the corresponding figures were 3 deaths per 100,000 with a highest arguable estimate of 20 and a lowest that was "insignificant;" at this level of exposure, the risk for chrysotile was "probably insignificant" with a highest arguable estimate of 1 death per 100,000.

A review and meta-analysis of the risk of pleural mesothelioma from environmental exposure to asbestos by Bourdes et al. was published in 2000 (Bourdes V, Boffetta P, Pisani P.

Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. Eur J Epidemiol 2000;16:411-7). These authors identified eight relevant studies on the risk of pleural mesothelioma from household or neighborhood exposures. These authors found the relative risk of pleural mesothelioma from household exposure ranged between 4.0 and 23.7 with a summary risk estimate of 8.1 (95% confidence interval: 5.3-12); and for neighborhood exposures the relative risk ranged between 5.1 and 9.3 with a summary estimate of 7.0 (95% confidence interval: 4.7-11). Bourdes et al., stated their review suggested a substantial increase in risk of pleural mesothelioma following high environmental exposure to asbestos, but the data was insufficient to estimate the magnitude of risk at the level of environmental exposure commonly experienced by the general population in industrial countries.

Pan et al. concluded their data supported the hypothesis that residential proximity to naturally-occurring asbestos was significantly associated with increased risk of malignant mesothelioma in California (Pan XL, Day HW, Wang W, Beckett LA, Schenker MB. *Residential proximity to naturally occurring asbestos and mesothelioma risk in California.* Am J Respir Crit Care Med 2005;172:1019-25.

The 1998 WHO/IPCS monograph on chrysotile titled *Environmental Health Criteria 2003: Chrysotile Asbestos* stated in the summary section on page 144 that chrysotile asbestos posed an increased risk for the development of lung cancer and mesothelioma and that no threshold of exposure had been delineated for the carcinogenic risk.

The British Thoracic Society also came to a similar conclusion (British Thoracic Society Standards of Care Committee. Statement on malignant mesothelioma in the United Kingdom. Thorax 2001;56:250-265).

The study of pleural mesotheliomas based on the Swedish Family Cancer Database stated there was an increasing age-adjusted incidence of mesothelioma over the period 1961-1998, not only for occupations expected to be associated with asbestos exposure, but also in professional groups and even farmers (Hemminki K, Li X. *Time trends and occupational risk factors for pleural mesothelioma in Sweden.* J Occup Environ Med 2003;45:456-61).

The review article by Hillerdal in 1999 concerning nonoccupational exposure to asbestos concluded mesothelioma developed as a consequence of low levels of exposure to asbestos (Hillerdal G. *Mesothelioma: cases associated with non-occupational and low dose exposures.* Occup Environ Med 1999;56:505-13).

Iwatsubo et al. found the odds ratio for mesothelioma occurred at very low doses and their data suggested a no threshold model (Iwatsubo Y, Pairon JC, Boutin C, et al. *Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study.* Am J Epidemiol 1998;148:133-42).

A case-referent study reported by Rödelsperger et al. stated the authors found an odds ratio for mesothelioma greater than 4.5 with lung tissue asbestos fiber concentrations in the range of 100,000-200,000 fibers longer than 5 µm per gram of dry lung tissue, and an odds ratio for mesothelioma of about 2 or more recorded for lower lung tissue asbestos fiber concentrations in the range of 50,000-100,000 fibers longer than 5 µm per gram of dry lung tissue (Rödelsperger K, Woitowitz HJ, Bruckel B, et al. *Dose-response relationship between amphibole fiber lung burden and mesothelioma.* Cancer Detection Prevention 1999;23:183-93). In addition, Rödelsperger et al. found an odds ratio of 7.9 with low exposures in the range of anything more

than zero to 0.15 fibers/cc years (Rödelsperger K, Jöckel K-H, Pohlabein H, et al. *Asbestos and man-made vitreous fibres as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study.* Am J Ind Med 2001;39:262-75).

Magnani et al. in a tri-nation case-referent analysis found a moderate to high probability of non-occupational exposure to asbestos in the development of mesothelioma (Magnani C, Agudo A, Gonzalez CA, et al. *Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos.* Br J Cancer 2000;83:104-11).

Hodgson and Darnton estimated the relative potencies for crocidolite, amosite and chrysotile for mesothelioma induction was roughly 500:100:1 respectively (Hodgson JT, Darnton A. *The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure.* Ann Occup Hyg 2000;44:565-601). However, the report by Leigh and Robinson concluded, based on lung tissue amphibole fiber concentrations allowing for clearance half-lives, that the potency ratio for crocidolite, amosite and chrysotile was 26:14:1 respectively (Leigh J, Robinson BWS. *The history of mesothelioma in Australia, 1945-2001.* In: Robinson BWS, Chahinian AP, eds. *Mesothelioma.* London: Martin Dunitz; 2002:55-86).

Another widely-cited set of potency ratios reported in the literature was 30:15:1 for crocidolite, amosite and chrysotile, respectively (World Trade Organization Dispute Settlement Report WT/DS135. *European Communities – Measures concerning asbestos and asbestos-containing products.* Geneva: WTO;2000. See also WTO Dispute Settlement Reports 2001: Volume VIII: Pages 3303-4047 [DSR 2001:VIII]. Cambridge: Cambridge University Press; 2004).

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. As stated previously, 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 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 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 was 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;* and Suzuki Y, Yuen SR, Ashley R. *Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int J Hyg Environ Health 2005;208:201-210).*

Boutin et al. suggest 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).* With respect to black spots, Mitchev et al. stated it had been suggested the specific areas of the parietal pleura absorbed and retained inorganic particles from the pleural space, including carbon pigments and asbestos fibers, and could be starting points for pathologic changes induced by mineral fibers (Mitchev K, Dumortier P, De Vuyst P. *Black spots and hyaline pleural plaques on the parietal pleura of 150 urban necropsy cases. Am J Surg Pathol 2002;26:1198-1206).* The authors stated their purpose was to study the distribution of black spots, their microscopic appearance, and the possible relationship to pleural plaques in the parietal pleura of 150 consecutive necropsies of urban dwellers (mean age 67.7 ± 12.9 years) were examined. Black spots were stated to have been observed in 92.7% of the cases and were predominantly located in the lower costal and diaphragmatic zones and could correspond to the anatomic distributions of structures involved in pleural cavity clearance. Black spots correlated with sex (M > F) and age (old > young) and there was no relationship between the predominant locations of black spots and hyaline pleural plaques. The authors concluded black spots were present in the parietal pleura of the vast majority of the urban population and were more common in men and in elderly populations. The authors stated black spots were spread throughout the parietal pleura, but showed a topographic predominance on the paravertebral and axillary costal zones and in the diaphragmatic zones and could not be superimposed with the hyaline pleural plaques. The authors concluded the mechanisms of fiber migration and the exact pathogenic role of fiber characteristics in asbestos-related pleural disease remained opened.

Muller et al. reported on the results of the morphological and energy dispersive x-ray analysis of 12 black spots (4 surgical and 8 autopsy specimens) located in the parietal pleura (Muller KM, Schmitz I, Konstantinidis K. *Black spots of the parietal pleura: morphology and formal pathogenesis. Respiration 2002;69:261-7).* The authors stated black spots of the pleura developed in close correlation to lymphatic channels and blood vessels. Black spots were characterized by mild fibrosis and an inflammatory reaction to the incorporated foreign particles. The authors stated the connective tissue could result in the formation of hyaline granulomas. Aluminum, silicone and sometimes fibers were found in such areas. The authors concluded there were hints for an increased proliferation of mesothelial cells in some areas with black spots, although their findings did not support the classification of black spots as being an obligate early lesion in the development of malignant mesothelioma.

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.

Mesothelioma summary:

1. Mesothelioma is a fatal cancer whose only epidemiologically known cause is exposure to asbestos fibers. The latency period for mesothelioma is between 10 and 70 years.
2. All types of asbestos fibers cause mesothelioma – there is no type of asbestos fiber which does not cause mesothelioma (WHO policy paper: *Elimination of asbestos-related diseases*).
3. Mesothelioma can be caused by very brief exposures to very low concentrations of asbestos fibers – there is no level of exposure below which mesothelioma cannot arise (Hillerdal G. *Mesothelioma: cases associated with non-occupational and low dose exposures.* Occup Environ Med 1999;56:505-513).
4. It is the cumulative exposure to asbestos which causes disease and, for this reason, any identifiable exposure to asbestos can cause or contribute to the development of mesothelioma.
5. Mesothelioma can arise from household or bystander exposure or in persons who work in occupations not typically associated with exposure to asbestos. (Joubert L, Seidman H, Selikoff IJ. *Mortality experience of family contacts of asbestos factory workers.* Ann NY Acad Sci 1991;643:416-418.)

LUNG CANCER

Lung cancer is the second major disease identified to be caused by asbestos. Lung cancer associated with asbestosis 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. *Über 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 cancer 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 – asbestos modifies 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 – lung cancer risk is increased only when the inhaled fiber burden falls into the range recorded for asbestosis; and H3 – any inhaled dose of asbestos has 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. Recent studies support the idea that asbestos concentration and not asbestosis is a critical factor for associating lung cancer to asbestos. Henderson et al. evaluated the published literature between 1997 and 2004 concerning lung cancer and asbestos and stated the prevailing evidence strongly supported the cumulative exposure model (Henderson DW, Rödelberger K, Woidowitz H, Leigh J. *After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997-2004*. Pathology 2004;36:517-550).

Cullen et al. concluded that among current and former smokers exposed occupationally to asbestos, the risk of lung cancer increase with increased exposure duration, even in persons without clinical evidence of asbestosis (Cullen MR, Barnett MJ, Balmes JR, et al. *Predictors of lung cancer among asbestos exposed men in the beta-carotene and retinol efficacy trial*. Am J Epidemiol 2005;161:260-270).

Reid et al. studied former workers and residences of Wittenoom with known amounts of asbestos exposure (Reid A, de Klerk N, Ambrosini GL, et al. *The effect of asbestosis on lung cancer risk beyond the dose related effect of asbestos alone.* Occup Environ Med 2005;62:885-889). Between 1990 and 2002 there were stated to have been 58 cases of lung cancer. The authors concluded there was an increased risk of lung cancer with increasing exposure in those without asbestosis and that asbestosis was not a mandatory precursor for asbestos-related lung cancer. The authors stated the findings supported the hypothesis that it was the asbestos fibers per se that caused lung cancer, which could develop with or without the presence of asbestosis. It has also become apparent that bilateral pleural plaques are associated with an increased risk for the development of lung cancer at a relative risk of 2. This probably does not have anything to do with plaques, but probably is related to the fact that people who have more plaques have higher asbestos concentrations in their lung tissue.

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;89:20-26) 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 amphibole 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 amphibole 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. reviewed literature between 1997 and 2004 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 (Henderson DW, Rödelberger K, Woidowitz H, Leigh J. *After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997-2004.* Pathology 2004;36:517-550).

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 and other tobacco products.

Lung cancer summary:

1. All types of asbestos fibers cause lung cancer – there is no type of asbestos fiber which cannot cause lung cancer.
2. It is the cumulative exposure to asbestos which causes disease and, for this reason, any identifiable exposure to asbestos can cause or contribute to the development of lung cancer provided the patient has been exposed to a sufficient dose of asbestos to attribute the lung cancer to the asbestos exposure. In my opinion, lung cancer can be attributed to asbestos exposure if the patient has one year of heavy occupational exposure to asbestos (e.g. shipyard workers and construction workers who were on site during the spraying of asbestos insulation) or five years of more moderate asbestos exposure (e.g. sheet metal workers and carpenters).
3. Lung cancer can be attributed to asbestos exposure even in the absence of radiologically detectable asbestosis.
4. Asbestos exposure combined with smoking is much more likely to increase the risk of developing lung cancer than either smoking or asbestos exposure alone.

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).

Several studies have shown an association between GI tract cancers and asbestos. Jansson et al. showed an association between the development of esophageal adenocarcinoma and exposure to asbestos with an incidence rate ratio of 4.5 (95%) and a confidence interval of 1.4-14.3 (Jansson C, Johansson AL, Bergdahl IA, et al. *Occupational exposures and risk of esophageal and gastric cardia cancers among male Swedish construction workers*. Cancer Causes Control 2005;16:755-764). Varga et al. stated the mechanism of cogenotoxic action between ingested amphibole asbestos fibers and benzo[a]pyrene via tissue specificity studies using comet assay showed high levels of DNA strand breaks in cells prepared from the omentum and intestine and demonstrated a significant potentiating effect of the absorbed carcinogen on the induction of DNA damage in omentum (Varga C, Horvath G, Timbrell V. *On the mechanism of cogenotoxic action between ingested amphibole asbestos fibres and benzo[a]pyrene: II. Tissue specificity studies using comet assay*. Cancer Lett 1999;139:173-176). Their results were stated to support the molecular model of asbestos carcinogenesis, including both asbestos-induced deletions and mutations caused by a mutagen carried by the same fibers.

Jakobsson et al. stated their aim was to investigate the association between exposure to mineral fibers and dust, and cancer in subsites within the large bowel. They found an increased incidence of cancer in the right colon in asbestos cement and cement workers. The distribution of cancers within the colon was stated to have been noticeably different from that in other blue collar workers, indicating their findings could not be explained by socioeconomic confounding factors alone (Jakobsson K, Albin M, Hagmar I. *Asbestos, cement, and cancer in the right part of the colon*. Occup Environ Med 1994;51:95-101).

With respect to head and neck cancers, Purdue et al. studied occupational exposures and head and neck cancers among Swedish construction workers and concluded there was an increased incidence of laryngeal cancers in asbestos-exposed individuals with a relative risk of 1.9 and a

confidence interval of 1.2-3.1 (Purdue MP, Jarvholm B, Bergdahl IA, Hayes RB, Baris D. *Occupational exposures and head and neck cancers among Swedish construction workers. Scand J Work Environ Health* 2006;32:270-275).

Wunsch studied the epidemiology of laryngeal cancer in Brazil and stated the most important risk factors involved in the genesis of laryngeal cancer were tobacco smoking and alcohol intake with other occupational exposures such as asbestos, strong inorganic acids, cement dust and free crystalline silica also being associated with the genesis of laryngeal cancer (Wunsch FV. *The epidemiology of laryngeal cancer in Brazil. Sao Paulo Med J* 2004;122:188-194).

Dietz et al. stated that investigators found that after adjustment for tobacco and alcohol intake, a significant elevated odds ratio could be demonstrated for persons that were exposed to cement during their work as building and construction workers (Dietz A, Ramroth H, Urban T, Ahrens W, Becher H. *Exposure to cement dust, related occupational groups and laryngeal cancer risk: results of a population based case-control study. Int J Cancer* 2004;108:907-911). The authors concluded there was good evidence that asbestos was an independent risk factor for laryngeal cancer.

Berrino et al. stated that significant elevated risk adjusted for nonoccupational variables (smoking, alcohol consumption and diet) and other occupational exposures were consistently found for organic solvents and asbestos (odds ratio 1.6, 1.0-2.5). The authors concluded that exposure to solvents was associated with an increased risk of hypopharyngeal/laryngeal cancer and their results provided additional evidence of an excess risk of hypopharyngeal/laryngeal cancer for exposure to asbestos (Berrino F, Richiardi L, Boffetta P, et al. *Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland. Cancer Causes Control* 2003;14:213-223).

Another study looking at occupational hazardous substance exposure and nutrition for pharyngeal and laryngeal carcinomas stated a case-control study to investigate occupational risk factors for squamous cell carcinoma of the oral cavity, pharynx and larynx was conducted (Maier H, Tisch M, Kyrberg H, Conradt C, Weidhauer H. *Occupational hazardous substance exposure and nutrition. Risk factors for mouth, pharyngeal and laryngeal carcinomas? HNO* 2002;50:743-752). The study included 209 male cancer patients and 110 male control persons without known malignant disease who were matched for age, alcohol consumption and tobacco consumption. The authors stated the educational level in the cancer group was significantly lower (17.2% of the cancer patients and 7.3% of the control persons) having not completed their professional training. An increased cancer ratio was observed for workers exposed to asbestos with an odds ratio of 8.7 ($p = 0.004$).

A committee on asbestos studied health effects regarding certain cancers and concluded the evidence was sufficient to infer a causal relationship between asbestos and laryngeal cancer (*Asbestos selected cancers. Washington DC, National Academic Press* 2006:187-188).

NON-NEOPLASTIC DISEASES CAUSED BY ASBESTOS

Non-neoplastic diseases caused by asbestos include asbestos-induced pleural effusion; hyaline pleural plaques; diffuse pleural fibrosis; round (rounded) atelectasis; pleural plaque spots; asbestosis; and localized and unusual benign conditions. Pathologic and other information concerning these conditions are discussed in detail in Chapter 27 of Pulmonary Pathology (Hammar SP, Dodson RF. *Asbestos*. Chapter 27. In: Dail DH, Hammar SP, eds., 3rd Ed. *Pulmonary Pathology*. New York: Springer-Verlag. *To be published in 2007*).

Asbestos-induced pleural effusion occurs primarily in older males who were often last exposed to asbestos 15 to 20 years prior to when the effusion occurred. The effusion is usually hemorrhagic and exudative and may be painful and is not infrequently associated with asbestos-induced hyaline pleural plaques and asbestosis. The effusion frequently contains a significant number of eosinophils. The effusion may last for weeks to several months and spontaneously resolve. Diagnosis of an asbestos-induced pleural effusion is somewhat a diagnosis of exclusion, since other conditions such as infection can cause a similar type of exudative effusion.

Hyaline pleural plaques are discrete, yellow-white, irregularly shaped, frequently calcified structures most frequently involving the parietal pleura and most frequently involving the parietal pleura covering the diaphragm and the parietal pleura in the posterior lower portion of the chest cavity. These structures are composed of dense fibrous tissue and frequently undergo calcification. Histologically, they show a basket weave pattern. They are almost always associated with elevated concentrations of asbestos in lung tissue and the plaques themselves contain asbestos fibers, the most common of which is chrysotile. In most instances, the plaques do not cause symptoms, although when they involve 50% or more of the parietal pleural surface, they can be associated with restrictive lung disease. The mechanism by which plaques develop is not well understood, but probably is related to localized inflammation caused by asbestos which then resolves. The exact time it takes for plaques to form is not known and the exact concentration of asbestos that it takes to form plaques is also not known, however, in general, there is a wide range of concentration of asbestos one finds in the lungs of people who have plaques.

Diffuse pleural fibrosis is relatively common in patients occupationally exposed to asbestos, although the exact incidence is not well documented. It occurs less frequently than hyaline pleural plaques and usually has a latent period of about 15-40 years. The morphology of diffuse pleural fibrosis is variable and depends on the severity of the disease. The visceral pleura is most frequently involved and shows varying degrees of whitish opacification. Microscopically, there is scarring, increased vascularity and inflammation. Occasionally, diffuse pleural fibrosis and hyaline pleural plaques co-exist. Some authors have suggested that visceral pleural fibrosis may be a direct extension of parenchymal fibrosis. If so, diffuse pleural fibrosis can be diagnosed radiographically as asbestosis, especially if there is underlying scarring of the lung parenchyma.

Occasionally, both the visceral pleura and the parietal pleura can scar to the point where they produce a condition referred to as *fibrothorax*, in which the lung is encased by a dense rind of fibrous tissue that macroscopically resembles mesothelioma, but microscopically is benign.

Round (rounded) atelectasis is a condition most frequently observed by radiologists in persons occupationally exposed to asbestos. Most persons who have round atelectasis are asymptomatic and, radiographically, have a unilateral, round, peripheral density often in the right lower and/or right middle lobes with one or more curvilinear shadows that radiate from this density towards the hilum of the lung. This lesion can be misinterpreted as a neoplasm. Various theories have been suggested with respect to the pathogenesis of round atelectasis.

Boutin et al. described black spots as areas where long amphibole fibers accumulated in association with carbonaceous dust and appeared black on the parietal pleura (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). These were hypothesized to be the starting point for asbestos-related neoplastic and inflammatory conditions. Specifically, the authors suggested that mesothelioma originated in these black spots due to amphibole fibers. I have never seen a black spot on the parietal pleura of about 500 autopsies done on persons who were exposed to asbestos. If this reflects a different type of dust exposure in the United States versus elsewhere is uncertain.

Mitchev et al. evaluated the entire parietal pleura from 150 consecutive necropsies of urban dwellers for the prevalence, anatomic distribution and macroscopic appearance of black spots and hyaline pleural plaques (Mitchev K, Dumortier P, De Vuyst P. *Black spots and hyaline pleural plaques on the parietal pleura of 150 urban necropsy cases.* Am J Surg Pathol 2002;26:1198-1206). Black spots consisted of deposits of opaque particles located under and intact mesothelial layer often in association with chronic inflammatory cells; namely, plasma cells, lymphocytes and macrophages. They were stated to have been found predominantly in the lower paravertebral zones on the spine, or close to it, on the central tendinous parts of both diaphragms, and around the anterior axillary lines. They were stated to have been observed in 92.7% of cases and more frequently in males and those of advanced age. The authors concluded there was no correlation between the locations of anthracotic spots and pleural plaques. Pleural plaques were observed predominantly in areas of parietal pleura with a lower prevalence of black spots. Black spots were stated to be related to structures responsible for lymphatic drainage of the pleural cavity and specifically reflected "clogged sewage system," marking the places of maximal pleural re-absorption.

More recently, Muller et al. stated black spots were described to represent areas of coal dust accumulation with an increased incorporation of asbestos fibers (Muller KM, Schmitz I, Konstantinidis K. *Black spots of the parietal pleura: morphology and formal pathogenesis.* Respiration 2002;69:261-267). They evaluated the morphology and energy dispersive x-ray analysis of 12 black spots located in the parietal pleura. Black spots were stated to have developed in close correlation to lymphatic channels and blood vessels. Their formal pathogenesis was stated to have been characterized by a mild fibrosis and inflammatory reaction to the incorporated foreign particles. The proliferation of connective tissue could result in the formation of hyaline granulomas. Aluminum, silicone, and sometimes fibers were found in such areas and the mesothelial cells were stated to occasionally be irritated. The authors concluded that although there were hints for an increased proliferation of mesothelial cells in some areas with black spots, their findings did not support the classification of black spots as an obligate early lesion in the development of malignant mesothelioma.

Cases of severe pulmonary asbestosis in association with exposure to asbestos were described in the early 1900s. In 1924, Cooke coined the term "asbestosis" and published a detailed pathologic description of the disease. There have been several reports concerning the morphology of asbestosis. The term *pleural asbestosis* has sometimes been used to refer to

scarring of the pleura caused by asbestos and, in my opinion, this term should be avoided because it is confused with parenchymal scarring of the lung caused by asbestos, which is properly referred to as *asbestosis*. The macroscopic appearance of asbestosis depends on the severity of the disease. The disease has been categorized into four histologic grades - grade 1 being the least severe and grade 4 being the most severe.

Grade 0	No fibrosis is associated with bronchioles
Grade 1	Fibrosis involves wall of at least one respiratory bronchiole with or without extension into the septa of the immediately adjacent layer of alveoli; no fibrosis is present in more distant alveoli
Grade 2	Fibrosis appears as in grade 1, plus involvement of alveolar ducts or two or more layers of adjacent alveoli; there still must be a zone of nonfibrotic alveolar septa between adjacent bronchioles
Grade 3	Fibrosis appears as in grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchioles have thickened, fibrotic septa; some alveolar may be obliterated completely
Grade 4	Fibrosis appears as in grade 3, but with formation of new spaces of a size larger than alveoli, ranging up to as much as 1 cm; this lesion has been termed <i>honeycombing</i> ; spaces may or may not be lined by epithelium

The pathogenesis of asbestosis involves inflammation with release of various mediators that eventually stimulate the fibroblasts and interstitium of the lung to produce more collagen and elastin, which, if the disease is progressive, can over time obliterate the lung, resulting in diffuse interstitial fibrosis with honeycombing. It should be recognized there is a wide variation in the amount of asbestos one finds in the lung tissue of people with various grades of asbestosis. The reason for this is not well understood, but, like any other asbestos-related disease, there appears to be individual susceptibility to the development of the disease. The clinical features of asbestosis depend on its severity. Those with grade 3 and 4 asbestosis usually have significant shortness of breath and dyspnea on exertion and have distinct radiographic abnormalities. The primary differential diagnosis of asbestosis is idiopathic pulmonary fibrosis (usual interstitial pneumonia). Pathologically, there appears to be more fibroblastic foci in cases of usual interstitial pneumonia than there is asbestosis.

Since a significant percentage of individuals exposed to asbestos are also cigarette smokers, there has been some problem in determining the exact relationship between cigarette smoke and asbestos in causing interstitial fibrosis. Cigarette smoke has been found experimentally to inhibit clearance of asbestos in the lungs of guinea pigs. Cigarette smoke can also cause squamous metaplasia of the lining of the respiratory epithelium of the bronchi, which can inhibit clearance. Some studies have shown that cigarette smoke causes an increased penetration of amosite into the airway walls in guinea pigs resulting in an increased concentration of fibers in the interstitium.

With respect to radiographic abnormalities, cigarette smoke has been suggested to cause an increase in small irregular opacities, although other studies have not shown any increase. The 2004 ATS document on environmental and occupational health issues concerning asbestos-related diseases (American Thoracic Society Documents. *Diagnosis and initial management of nonmalignant diseases related to asbestos*. Am J Respir Crit Care Med 2004;170:691-715) stated that asbestosis was more prevalent and advanced for a given duration of exposure in cigarette smokers, presumably due to reduced clearance of asbestos fibers from the lung. Although some studies suggested that smokers without dust exposure showed occasionally

irregular radiographic opacities on chest films, smoking alone was stated to not cause changes of asbestosis. Therefore, smokers and ex-smokers were stated to have a higher frequency of asbestos-related opacities on their chest radiographs than did non-smoking asbestos workers in all profusion categories. The 2004 ATS document further stated cigarette smoking did not affect asbestos-induced pleural fibrosis.

As stated previously, the clinical features of asbestosis depend on the severity of the disease. Those with grade 3-4 asbestosis are usually symptomatic, with the most common symptom being dyspnea on exertion. There is an increased incidence of clubbing of the fingers, although the diagnostic usefulness of this finding is minimal. Most patients with pathologic grade 3-4 asbestosis have Velcro rales. Pulmonary function tests usually show restrictive lung disease with a decrease in total lung capacity and forced vital capacity. Hypoxemia may or may not be present at rest, or may develop with exercise, and the diffusing capacity is usually decreased.

In 1986 the American Thoracic Society (ATS) proposed the following criteria for the clinical diagnosis of asbestosis: 1) a reliable history of exposure to asbestos; 2) an appropriate latent interval between exposure and detection of asbestosis; 3) chest roentgenographic evidence of type "s," "t" or "u" small irregular opacities with a profusion of 1/1 or greater; 4) a restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal; 5) a diffusing capacity below the lower limit of normal; and 6) bilateral or late pan inspiratory crackles at the posterior lung bases not cleared by coughing. In 2004, the ATS document lists the criteria for diagnosing lung diseases, including asbestosis, and commented on the 1986 criteria. This is shown in the table below. In 2004 the ATS stated that a profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal.

Table 27-15. Criteria for diagnosis of nonmalignant lung disease related to asbestos.

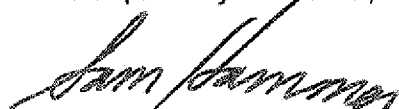
1986 Guidelines	2004 Guidelines	Comparison and Notes
	Evidence of structural change, as demonstrated by one or more of the following:	Demonstrates the existence of a structural lesion consistent with the effects of asbestos. The criteria outlined in the 1986 guidelines were most explicit for asbestosis.
Chest film (irregular opacities)	Imaging methods	Chest film, HRCT, and possibly future methods based on imaging. The 1986 guidelines specified ILO classification 1/1.
Pathology (College of American Pathologists)	Histology (College of American Pathologists)	Criteria for identifying asbestosis on microscopic examination of tissue are unchanged.
Consistent time interval	Evidence of plausible causation, as demonstrated by one or more of the following:	
Occupational and environmental history	- Occupational and environmental history of exposure (with plausible latency) - Markers of exposure (e.g., pleural plaques) - Recovery of asbestos bodies	The 2004 guidelines are not limited to lung tissue, consider the role of BAL to be established, and deemphasize fibers because they are difficult to detect and a systematic analysis for asbestos fibers is not generally available.
Asbestos bodies or fibers in lung tissue		
Rule out other causes of interstitial fibrosis or obstructive disease	Exclusion of alternative diagnoses	The 1986 guidelines primarily addressed asbestosis but mentioned smoking as a cause of obstructive disease. Implicit in the article, however, is that nonmalignant diseases presenting similarly to asbestos-related disease should also be ruled out.
"Evidence of abnormal test"	Evidence of functional impairment, as demonstrated by one or more of the following:	Functional assessment is not required for diagnosis but is part of a complete evaluation. It contributes to

Crackles, bilateral, not cleared by cough	• Signs and symptoms (including crackles)	diagnosis in defining the activity of disease and the resulting impairment. Signs and symptoms are not specific for diagnosis but are valuable in assessing impairment.
Restrictive disease	• Change in ventilatory function (restrictive, obstructive patterns in context or disease history)	The 1986 criteria admitted the possibility of obstructive disease; the 2004 criteria address this specifically.
Reduced diffusing capacity	• Impaired gas exchange (e.g., reduced diffusing capacity) • Inflammation (e.g., by bronchoalveolar lavage)	The 1986 guidelines noted possible utility of bronchoalveolar lavage and gallium scanning but considered them to be experimental techniques. The 2004 guidelines exclude gallium scanning, suggest that additional indicators of active inflammation may become useful in future.
	• Exercise testing	

Kipen et al. stated that of 400 confirmed deaths from lung cancer, a chest radiograph suitable for determining evidence of pneumoconiosis was obtainable in 219 (Kipen HM, Lilis R, Suzuki Y, et al. *Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation.* Br J Ind Med 1987;44:96-100). Of these cases, 138 also had a tissue specimen that was suitable for histologic study to determine the extent of histological fibrosis. There was stated to be a significant, albeit limited correlation between the radiographic and histologic findings ($r = 0.27$, $p < 0.0013$). All 138 cases had histologic evidence of parenchymal fibrosis. In 25 cases (18%), there was no radiographic evidence of parenchymal fibrosis. In 10 cases (7%), both parenchymal and pleural disease were undetectable on the radiograph. The authors concluded a negative chest radiograph does not exclude the presence of interstitial fibrosis (asbestosis) in a substantial proportion of insulation workers previously exposed to asbestos who developed lung cancer. This study should be kept in mind, especially in people who are symptomatic and whose chest radiographs do not show changes suggestive of asbestosis.

Localized and unusual pulmonary diseases occur in persons occupationally exposed to asbestos. These include organizing pneumonia-bronchiolitis obliterans (BOOP); desquamative interstitial pneumonitis-like change; asbestos-cigarette smoke-induced interstitial lung disease; aspergillus infection in asbestos-exposed individuals; granulomatous inflammatory-type changes; and lymphocytic interstitial pneumonia. In the 2004 ATS document, they referred to the organizing pneumonia-type changes as asbestomas. These are usually misinterpreted radiographically as lung cancers and, perhaps not surprisingly, they show an increased activity when evaluated by positron emission tomography (PET scans).

Respectfully submitted,



Samuel P. Hammar, M.D.
Director, Diagnostic Specialties Laboratory
700 Lebo Blvd.
Bremerton, WA 98310
Phone: 360-479-7707
Fax: 360-479-7886