Toward a Defense of Mesothelioma Cases on Causation: Low Doses and Genetics
by Mark Zellmer

Introduction
Today’s defendants in asbestos litigation often face plaintiffs’ claims that they have contracted mesothelioma from exposure to low or even doubtful doses of asbestos. If the mesothelioma looks to be spontaneous (idiopathic) or the result of an exposure so low that it will not cause the disease or the mesothelioma, genetics may provide the alternate explanation to satisfy the jury about why plaintiff or decedent has mesothelioma.

Genetic Predisposition: Inherited Cancer Syndromes as a Cause of Mesothelioma Independent of Asbestos

Looking to Restatement (Second) of Torts, Section 432(2) (1965), causation is not proven and in fact rebutted “if the harm would have been sustained even if the actor had not been negligent.” Five to ten percent of tumors occur as a result of monogenic predispositions while another 30-50% occurs due to polygenic predispositions. Lubinski J. et al. “Molecular Basis of Inherited Predisposition for Tumors.” Acta Biochimica Polonica. Vol. 49(3) (2001) at 571. Mesothelioma, caused by one of a number of genetic predispositions, is not any different.

TP53/Li-Fraumeni
In 1969, Frederick Li and Joseph Fraumeni first described the most clearly established, hereditary, tumor predisposition. It is an autosomal dominant pattern of various tumors including soft tissue sarcoma, breast cancer, brain tumors, adenocortical carcinoma, leukemia, lymphoma, and melanoma as well as lung, prostate, pancreatic, and ovarian, kidney, testicular, laryngeal, head and neck cancers. Li F. et al. “A Cancer Family Syndrome in Twenty-four Kindred.” Cancer Research. Vol. 48 (1988) at 5358. The Li-Fraumeni Syndrome, as it is now known, is a germline mutation in the TP53 gene which controls cell growth and division and “encodes” or produces the tumor suppressor protein p53. Fifty percent of individuals with the TP53 mutation developed some sort of cancer by age 30. The risk over a lifetime in men is 70% while almost 100% in women. Li-Fraumeni Syndrome is now accepted as leading to malignant mesothelioma, particularly peritoneal mesothelioma. Celeen W. “Malignant Peritoneal Mesothelioma in a Patient with Li-Fraumeni Syndrome.” Journal of Clinical Oncology. Vol. 29(17) (2011) at 503

BAP1
In 2010 Carbone et al identified BAP1 as a germline mutation creating an autosomal dominant cancer syndrome. Carbone M. et al. “BAP1 Cancer Syndrome: Malignant Mesothelioma, Uveal and Cutaneous Melanoma and MBAITs.” Journal of Transitional Medicine. Vol. 10 (2010) at 10.1186/1479-5876-10-179. BRCA1 the associated protein 1 (BAP1) constitutes a tumor suppressor gene located on chromosome 3p21. Its mutation was found to be associated with increased risk of malignant mesothelioma and other neoplasms. The prevalence of cancer among a BAP1-mutated cohort is seven times greater than among the non-mutated cohort, 63% compared to 9% respectively. Other cancers in this syndrome include melanoma (uveal and cutaneous), lung, breast, renal and MBAIT.

The question arises whether BAP1 is an independent factor in the cause of mesothelioma or whether asbestos is a necessary addition to cause the disease. Science has directed efforts to answer such questions. A group reviewed...
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Most of the talk about a special susceptibility to mesothelioma from low dose exposure comes from experiments on mice with the dominant BAP1 mutation. Of course what is found in animals may not apply to humans, particularly when the mice are exposed through direct injection into the peritoneum while human exposure almost invariably comes from inhalation. Most tellingly, finding an increased number of cases of peritoneal mesothelioma in mice from low doses is inconsistent with human experience. Prolonged and heavy exposure, not a low dose exposure, is necessary to cause peritoneal mesothelioma in humans.

**Bringing It Altogether: Industrial Hygiene, Family History and Genetic/Molecular Testing**

Methods of genetic testing include biochemical testing, molecular or direct and cytogenic testing. Obtaining the necessary blood or tissue for genetic testing will require a court order. Although drawing blood is of course minimally invasive, plaintiff may argue otherwise. A trial court confronted this issue in California faced with a young man claimed to be deathly afraid of needles. The court allowed the testing, including drawing blood, reasoning that the defendant had a right to present a defense. *San Francisco Examiner*, June 7, 1994 at www.nwitimes.com.

There are a number of steps in preparation of the defense.

- An industrial hygienist must calculate the dose.
- A medical expert should testify that the dose calculated by the hygienist is not sufficient to increase materially the risk of mesothelioma and in fact did not cause the mesothelioma.
- Experts must establish any family history of cancer among blood relatives as well as any prior or concurrent cancer suffered by plaintiff.
- Defendant should perform genetic testing on plaintiff’s tissues.
- Defendant must be prepared to present a genetics expert to opine that a genetic predisposition is the cause of plaintiff's mesothelioma.

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