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Asbestos

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A commentary article reprinted from the August 29, 2018 issue of Mealey's Litigation Report: Asbestos

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Commentary

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[Editor's Note: Thomas P. Bernier is a partner in Goldberg Segalla's Baltimore office and Chair of the Nanotechnology Practice Group — a subgroup of the Toxic Torts and Environmental Practice Group. Tom has spent more than three decades defending complex toxic tort actions, with particular concentration on claims alleging exposure to Legionella and other waterborne pathogens, asbestos, and mold. He is a frequent author and presenter on topics pertaining to his areas of practice, with two seminars recognized by the Maryland Institute for Continuing Professional Education of Lawyers (MICPEL) as "Best of MICPEL" seminars, and has been invited to speak about Legionella and Legionnaire's disease at conferences and seminars across the country. Oded Burger is an associate in Goldberg Segalla's Toxic Tort and Intellectual Property Practice Groups. Oded has nearly a decade of experience handling high-value toxic tort litigation involving a wide range of complex scientific issues, and has represented numerous clients across a variety of industries, including serving as regional trial counsel for a Fortune 500 automotive manufacturer. He has authored numerous successful and critical motions, including multiple post-trial motions to set aside verdicts based on plaintiffs' failure to meet scientific causation standards. Joe Cagnoli is Goldberg Segalla's Toxic Tort Practice Group Leader. Nationally recognized as a leading attorney in oil and gas and hydrofracturing matters, Joe frequently publishes and presents on this emerging area of environmental litigation. He has significant experience representing manufacturers of vehicles and commercial and industrial equipment in product liability and environmental matters involving benzene, asbestos, and other chemical exposures, and currently serves as lead defense counsel for a hydraulic fracturing company. Susan Van Gelder is a partner in Goldberg Segalla's Toxic Tort and Product Liability Practice Groups. With nearly 20 years' experience representing suppliers and manufacturers of asbestos-containing products, equipment and component parts in lawsuits spanning the Northeast, Susan has handled thousands of asbestos cases over the course of her career. In addition, Susan represents clients in traditional products liability cases and in a wide array of other toxic tort exposures including lead paint, mold, silica and coal tar pitch. Any commentary or opinions do not reflect the opinions of Goldberg Segalla LLP or LexisNexis®, Mealey Publications™. Copyright © 2018 by Thomas P. Bernier, Oded Burger, Joseph Cagnoli Jr., and Susan E. Van Gelder. Responses are welcome.]

After more than three decades of asbestos litigation, it is no wonder that judges and litigants have the false impression that the causation of mesothelioma is a well-settled matter. The presentation of individual asbestos cases as a single monolithic litigation is heralded by the tireless refrain of plaintiffs' experts: "Mesothelioma is a signature tumor for asbestos exposure." Indeed, this overly simplified view of causation is further driven by the plaintiffs' bar, who reflexively advocate for the consolidation of disparate cases premised solely on some sort of alleged exposure to asbestos. However, recent advances in genomics and epidemiology are providing

the defense bar with a new set of tools to challenge this one-size-fits-all etiological model. In this article, we explore the recent scientific advances related to non-asbestos causation defenses and the practical considerations of presenting those defenses in a courtroom.

One of the most significant recent developments in asbestos litigation has come from the field of genomics. Since 2011, over a dozen scientific papers have identified BAP1 and related mutations as factors capable of causing mesothelioma independently of any exposure to asbestos. Critically, the published findings do not establish a synergistic gene/environment interaction as a causal factor for the development of mesothelioma. In this article, we will explore both the practical considerations of readying a genetics-based defense as well as how the presentation of these recent scientific findings relates to the legal issues such as the eggshell plaintiff doctrine, foreseeability, and the duty to warn.

The harmful effects of ionizing radiation have long been recognized by medical researchers. However, recent scholarship has drawn an increasingly clear causal connection between therapeutic ionizing radiation and the development of secondary tumors including multiple forms of mesothelioma. The implications of these recent findings can be quite dramatic on asbestos litigation, as it is estimated that more than a third of all cancer patients undergo some form of radiation therapy. In this paper, we will provide practical advice on how to prepare the record for expert review through discovery while highlighting key challenges, including issues related to latency, dose response, and potential synergy with asbestos exposure.

Lastly, the paper will examine exposures to naturally occurring sources of elongate materials as potential alternative causation defenses. The dramatic clusters of mesothelioma cases in Turkish villages where naturally occurring erionite was used as a building material have received much attention in scientific literature. However, it is less well known that very high concentrations of erionite have been found in the Intermountain West of the United States from Oregon into Mexico and the Sierra Madre Occidental region. In this article, we explore the geological resources and analytical methods for evaluating potential exposure to naturally occurring sources of elongate materials as an alternative causation defense.

It is well recognized that approximately 20 percent of mesothelioma patients do not recall any exposure even after a detailed historical assessment. Plaintiffs' experts routinely speculate that those cases must have been caused by so-called "occult" exposures to asbestos. Here, we open the lid on a scientific toolbox that will help provide judges and juries with a more complete understanding of the causation issues they will be asked to evaluate.

Genetic Defenses

Fifteen years following the completion of the Human Genome Project, the use of genetics has finally come of age in toxic tort litigation. Litigants on both sides have begun raising arguments concerning the relationship between an individual's genetic predisposition to develop certain diseases and an array of potentially toxic exposures including tobacco,[1] benzene,[2] radiation,[3] and increasingly asbestos.[4] Researchers have now identified hundreds of genes as factors in carcinogenesis. With regard to mesothelioma, they include NF2, TP53, CDKNA2A, ALK, VISTA, BRCA1 & 2, and, most importantly, BAP1.

The gene encoding BRCA1 Associated Protein 1, more commonly referred to as BAP1, was first discovered in 1998.[5] BAP1 is an enzyme that regulates ubiquitin, a regulator protein that is centrally involved in both cell division and DNA transcription and repair. BAP1's regulation of ubiquitin allows it to function as both a tumor suppressor and metastasis suppressor. The impairment of the BAP1 gene has been linked to an inherited disorder known as the BAP1 tumor predisposition syndrome,[6] which increases the risk of developing a variety of cancerous and noncancerous tumors of the skin, eyes, kidneys, and mesothelium.[7] Despite this discovery and understanding of the existence and function of the BAP1 gene in 1998, it would be more than a decade before its connection to malignant mesothelioma would be understood.

In 2011, Dr. Joseph Testa and his colleagues published an article entitled *Germline BAP1 mutations predispose to malignant mesothelioma* in the journal, *Nature Genetics*. In this article, a causal connection between germline BAP1 mutations and the development of malignant mesothelioma was found for the first time.[8] Testa *et al.* described two families afflicted with multiple cancers who were found to have BAP1 mutations. Intriguingly, the subjects of the study had developed mesothelioma

without any reported occupational exposures to asbestos.[9] Those families were the subject of further scholarship in 2012, where it was reported that the BAP1 mutation was additionally causally related to uveal and cutaneous melanoma and melanocytic BAP1-mutated atypical intradermal tumors.[10] Thus, the work of Testa *et al.* is important as it defines not only the BAP1 mutation's connection to the development of malignant mesothelioma, but also the predisposition of an individual to develop that disease even in the absence of asbestos exposure—predominantly considered that condition's signature cause.

At present, it is estimated that between 1 and 8 percent of all spontaneous mesothelioma cases involve BAP1 germline mutations.[11] It is has also been reported that 6% of mesothelioma patients with a family history of cancer will carry a BAP1 germline mutation.[12] At least one additional study took a substantive look at the potential prevalence of the BAP1 mutation in the human population by assessing the probable geometric genealogical spread of the mutation. In 2015, a genealogic effort reported on approximately 80,000 BAP1 mutation carriers that descended from a single couple born in Germany in the early 1700s who had immigrated to North America.[13] The full breadth of the BAP1 mutation across society is a topic of ongoing scientific inquiry.

Understanding the fundamentals of the BAP1 mutation is critical to the utilization of this science to analyze the validity of a matter in which mesothelioma is alleged to have been caused by exposure to asbestos. There is a debate between mutation as the cause and mutation as the creation of mere susceptibility. In normal circumstances, an individual will have two functional copies of the BAP1 gene, each inherited from his or her parents. A person who is afflicted with a BAP1 germline mutation will inherit both a functional and a nonfunctional copy of the BAP1 gene. (Unfortunate offspring who inherit two nonfunctional copies of the BAP1 gene will not typically survive to term.) An individual with one functional copy of the BAP1 gene will typically remain healthy until their 40s when statistically a mutation will damage the only functional copy of the BAP1 gene, a process known as loss of heterozygosity. It is thought that while significant environmental interactions can contribute to the loss of the sole functional BAP1 gene that process can also occur spontaneously as a result of errors which occur during normal cellular division.[14] As a benchmark, it has been estimated that by the age of 15, the normal cellular division process will lead to a thousand such mutations.[15] Accordingly, it has been demonstrated that the risk of spontaneous mesotheliomas increase with age.[16]

Predisposition or Susceptibility

The spontaneous nature of loss of heterozygosity (BAP1 mutation as an independent cause) in individuals carrying a BAP1 germline mutation is supported on several levels. First, most of the types of cancers which are a part of the BAP1 tumor predisposition syndrome are thought to occur spontaneously and are not associated with any known environmental initiation factors. Secondly, it has been demonstrated that mice who have been bred to have only a single functional BAP1 gene have developed spontaneous tumors, including both pleural and peritoneal mesotheliomas, in the complete absence of any exposure to asbestos.[17] Thirdly, individuals who have BAP1 germline mutations who go on to develop mesothelioma tend to report negligible asbestos exposure histories.[18] The absence of a significant asbestos exposure history is particularly notable in relation to peritoneal mesothelioma patients with BAP1 germline mutations, as those malignancies do not normally occur in the absence of heavy exposures to amphibole asbestos. Fourthly, the incidence ratio between pleural and peritoneal mesothelioma rates amongst germline BAP1 mutation carriers is 1:1 as opposed to 8:1 in the general population.[19] Lastly, the BAP1 associated mesotheliomas have been described by atypical case studies such as a 16-year-old boy who developed peritoneal mesothelioma[20] and atypical survival patterns.[21] Notwithstanding the mounting evidence to the contrary, plaintiffs' experts continue to argue that BAP1 germline mutations create an extreme susceptibility to miniscule levels of asbestos exposure. Where plaintiffs have the burden of proof to show that the loss of heterozygosity was not the result of normal cellular division, it is unlikely that such unsubstantiated susceptibility theories can carry the day.

Beyond the issue of causation, a BAP1 germline mutation is relevant to the measure of damages since an individual with such a mutation would be expected to have a shorter lifespan. On average, a BAP1 carrier is thought to develop their first malignancy by the age of 55.[22] While not all malignancies identified as being a part of the BAP1 tumor predisposition syndrome are fatal, most unfortunately are. Additionally, mesothelioma patients

with BAP1 germline mutations tend to have a slower disease progression, which may impact the predicted future pain and suffering period.[23]

Genetic Testing

Testing for a hereditary influence on mesothelioma should be considered when the plaintiff meets one or more of the following criteria:

- 60 years or younger at the time of diagnosis
- Multiple primary tumors, particularly mesotheliomas, cutaneous melanomas, uveal melanomas, basal cell carcinomas, melanocytic tumors, renal cell carcinomas, paraganagliomas, cholangiocarcinomas, mucoepidermoid carcinomas, prostate cancers, breast cancers, lung cancers, meningiomas, ovarian cancers, or pancreatic cancers
- Any of the above cancers present in multiple genetically related relatives
- A diagnosis of peritoneal mesothelioma without a significant exposure to amphibole asbestos

Testing for a germline BAP1 mutation may be accomplished by a simple blood test.[24] Courts have recognized that while the drawing of blood is a relatively minor procedure, genetic testing has the possibility to reveal information about the plaintiff's long-term health and possibly the health of their family members.[25] Plaintiffs have had mixed results attempting to block genetic testing based on an argument that a BAP1 mutation only increases the susceptibility of developing cancer, and is therefore unlikely to lead to the discovery of relevant information.[26] In some states, statutes provide the ability to conduct blood testing.[27] Care should be exercised when selecting a laboratory to conduct genetic testing in confirming that the facility is both CLIA[28] and state[29] certified to perform such testing.

BAP1 at Trial

The first trial focusing on BAP1 was the Holly Ortwein case in Alemeda County California.[30] Tragically, Ms. Ortwein was the fourth member of her family to develop mesothelioma at the age of 55. She alleged that she developed pleural mesothelioma from limited take-home exposures she experienced as a child. The plaintiff attempted to block genetic testing sought by the defense. However, Judge Lee allowed the testing to proceed, reasoning in part that CertainTeed could legitimately argue that if Ms. Ortwein "was susceptible to mesothelioma such that she could have contracted the disease from levels of asbestos that CertainTeed would not reasonably have foreseen would cause the disease, then CertainTeed might not have had a duty to her on the grounds that the harm was not foreseeable."[31] Subsequent testing of Ms. Ortwein's lung tissue revealed that she carried a germline BAP1 mutation.

Ms. Ortwein's trial began before Judge Seligman in January 2016. Dr. Joseph Testa testified on behalf of the plaintiffs that because germline mutations have one functional copy of BAP1, the inherited genetic mutation cannot be said to have solely caused Ms. Ortwein's cancer. In offering such an opinion, he disavowed statements in an article he co-authored, expressly stating, "BAP1 mutation alone may be sufficient to cause mesothelioma."[32] On cross-examination, Dr. Testa conceded that none of the BAP1 carrier subjects who developed mesothelioma in the published literature had any occupational exposure to asbestos, but speculated that the trace presence of asbestos in some of the subjects' homes was evidence that carrying a BAP1 germline mutation leads to extraordinary susceptibility to asbestos. The case settled shortly thereafter.

The second BAP1-focused trial took place in a 2017 case, *Lamb v. CertainTeed Corporation*, in Contra Costa County Superior Court.[33] Mr. Lamb developed peritoneal mesothelioma at age 33. He alleged tertiary exposure from his father's work clothes, which he wore as a bystander to building demolition and construction. The plaintiff's counsel stipulated to testing after defendants filed a motion to compel the production of a blood sample, which subsequently confirmed a diagnosis of a BAP1 germline mutation. At trial, the plaintiff called Dr. Andrew Lowy, a surgical oncologist specializing in abdominal cancers. Dr. Lowy relied in part on a study in which he participated concerning the relationship between BAP1 mutations and the development of peritoneal mesothelioma. However, he conceded that none of the subjects of that study had exposure to asbestos. During CertainTeed's case in chief, they called Dr. Allan Feingold, who explained that the BAP1 mutation alone can cause cancer, and given Mr. Lamb's limited exposure history, it was far more reasonable to ascribe causation to his genetic condition than to an exposure to asbestos. While the jury returned a defense verdict in that matter, it was based on a rejection of the notion that CertainTeed was negligent. The jury never reached the question of whether

Mr. Lamb's peritoneal mesothelioma was caused by the alleged asbestos exposure or the product of the BAP1 mutation.

Radiation as an Alternative Cause

Radiation is a pancarcinogen and a recognized cause of mesothelioma. Evidence supporting this conclusion can be found in case reports, case series, and retrospective cohort studies linking radiation to malignant mesothelioma in patients previously receiving therapeutic irradiation of tumors, patients receiving radioactive thorium dioxide contrast medium (Thorotrast) for imaging studies, and workers exposed to prolonged lower levels of radiation as a result of their work in the nuclear energy industry.[34]

Thorium Dioxide

Thorotrast is a suspension that contains particles of the radioactive compound thorium dioxide, and was used as a radiocontrast agent in medical radiography throughout the 1930s and as late as the 1950s in the United States. Thorotrast produced excellent images because of its high opacity to X-rays. Unfortunately, thorium is retained in the body and is radioactive, emitting harmful alpha radiation as it decays with a biological half-life estimated to be 22 years.[35] A high over-incidence of cancers has been reported in patients treated with Thorotrast with latency periods usually in the range of 20 to 30 years.[36] Mauer and Egloff reported in 1975 on a 59-year-old female patient who died of peritoneal mesothelioma 36 years after she was injected with Thorotrast. The lack of exposure to asbestos was specifically noted.[37] In 1995, Stey *et al.* reported a case of malignant peritoneal mesothelioma in a 63-year-old male with a history of exposure to Thorotrast in 1945 and no known asbestos exposure.[38]

Occupational Exposure

Mesotheliomas have also been reported in an occupational setting in radiation technologists exposed to external gamma-ray emission and internal radionuclides.[39] The risk of mesothelioma was also elevated among British Atomic Energy workers employed between 1946 and 1990 at the Idaho National Engineering and Environmental Laboratory where nuclear processing and demolition occurred, emphasizing the significance of external scatter radiation at lower doses.[40]

Therapeutic Radiation

Far more research has been conducted into the potential for therapeutic radiation to cause secondary cancers. The history of radiation therapy can be traced back to experiments conducted soon after the 1895 discovery of X-rays when it was shown that exposure to radiation produced cutaneous burns.[41] Influenced by the medical application of caustic substances to treat various lesions, doctors began using radiation to treat growths produced by diseases such as lupus, basal cell carcinoma, and epithelioma.[42] Additionally, because radiation existed in hot spring waters reputed for their curative powers, it was marketed as a wonder cure for all sorts of ailments in patent medicine and quack cures. Medical science believed at that time that small doses of radiation would cause no harm and the harmful effects of large doses were temporary.[43] The widespread use of radium in medicine ended when longitudinal research exposed that physical tolerance was lower than expected and exposure caused long-term cell damage that could appear in carcinoma up to 40 years after treatment.[44] The use of radiation continues today as a treatment for cancer in radiation therapy.

As described by the National Cancer Institute, there are two main types of radiation therapy: external beam radiation therapy (EBRT), also known as teletherapy, and internal beam radiation therapy (IBRT), also known as brachytherapy.[45]

EBRT is radiation delivered from a distant source outside the body and directed at the patient's specific cancer site. There are several different radiation delivery system machines such as X-ray, Cobalt-60, linear accelerator, belatron, spray radiation, stereotactic radiosurgery, gamma knife, and proton and neutron beam.[46] The radiation oncologist decides which type of system is best suited to treat the patient's cancer. EBRT is the most commonly used option in treating tumors such as cancers of the head and neck area, breast, lung, colon and prostate.[47] The level of radiation depends on the tumor location. Low energy radiation does not deeply penetrate, and is therefore used to treat surface cancers such as skin cancer. High energy radiation is used to treat tumors found deeper within the body such as those in the head and brain.[48] Stereotactic radiation therapy (gamma knife) focuses high doses of radiation on small areas from several directions to achieve maximum tumor coverage with minimal exposure to surrounding areas.[49]

IBRT involves placing radiation sources as close to the tumor as possible, if not within the tumor itself. These

isotopes often take the form of seeds, wires, or rods. In the case of bony metastases, radioactive particles are attached to small molecules and introduced intravenously into the patient.[50] IBRT has proven to be particularly effective in treating cancers of the cervix, uterus, vagina, rectum, eye, and certain head and neck cancers. In some cases, it is used to treat cancers of the breast, brain, skin, anus, esophagus, lung, bladder, and prostate. On occasion, IBRT is used in conjunction with EBRT.[51]

The Carcinogenicity of Therapeutic Radiation Therapy

Ionizing radiation exerts a broad array of adverse effects on DNA, cell membrane lipids, and cell surface receptors that drive the oncogenic process when activated or mutated. It exerts its oncogenic effects through multiple pathways. These pathways include inducing expression of oncogenes, which causes double strand breaks of DNA, leading to mutations of one or more genes that are involved in DNA repair and control of the cell cycle. Further effects involve mutations to the all-important tumor suppressor gene p53, cell membrane sphingomyelin, and the activation of cell surface receptors that have a profound effect on cell survival pathways, primarily apoptosis — programmed cell death.[52]

Elderly patients are more susceptible to the adverse effects of radiation therapy, especially as it relates to double-strand DNA breaks, mutation of p53, decreased DNA repair after radiation-induced damage, and anti-apoptotic effects that enhance the survival of a cancer cell. Thus, in addition to directly inducing gene mutations which may lead to a second malignant neoplasm, radiation therapy may cause direct damage to normal tissue in the radiation field or in nearby tissue outside the direct field of radiation.[53]

Epidemiologic Data Linking Therapeutic Radiation Therapy for a Primary Malignancy and Increased Risk of Malignant Mesothelioma

An accepted precept in epidemiology is that well-designed and large epidemiology studies provide strong evidence to support cause and effect relationships and establish etiologic roles for specific agents. The 2007 study of Teta *et al.*, recently updated by Chang *et al.* in 2017, provides such data with respect to the mesotheliogenicity of therapeutic radiation.[54] These epidemiology studies and that of Li *et al.* (2010), provide data on malignant mesothelioma in patients with hematologic malignancies, primarily Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[55] Teta *et al.* reviewed the Surveillance, Epidemiology, and End Results (SEER) database over a 40-year period (1973-2014) to identify 47,219 patients with HL, 19,535 of whom were irradiated and 252,090 with NHL, of whom 52,454 were irradiated, with an eye toward whether any developed malignant mesothelioma as a second malignant neoplasm. They discovered that second primary mesotheliomas developed among 28 irradiated lymphoma patients and 59 non-irradiated patients suggesting that the risk of developing mesothelioma increased among HL and NHL patients treated with radiation therapy. After multivariate adjustment for time of treatment, age at diagnosis of lymphoma, sex, race, type of lymphoma, nodal status, and receipt of radiotherapy, the irradiated population remained significantly associated with a notably increased relative risk of 1.64 for a second primary mesothelioma. Of significance was the fact that the incidence of malignant mesothelioma did not increase in non-irradiated patients. The authors concluded, "The increase in second primary mesothelioma risk following radiotherapy for lymphoma is independent of several patient and disease characteristics and is higher with earlier treatment era and longer latency."[56] The updated findings of Chang *et al.* (2017) confirmed the earlier (2007) conclusion that therapeutic radiation in patients with lymphoma causes malignant mesothelioma.[57]

Further compelling epidemiologic support for Teta *et al.* comes from the Dutch study reported by DeBruin *et al.* (2009).[58] The Dutch investigators reviewed the risk of mesothelioma in 2,567 five-year survivors of HL and identified 13 cases of malignant mesothelioma occurring after radiation therapy. Of the 13 cases, eight were males and five were females. Twelve of the 13 received thoracic radiation. In the Dutch series, six of the 13 patients had no known exposure to asbestos, six had occupational exposure, and one had environmental exposure. The calculated risk of developing mesothelioma was 26-fold higher in patients with Hodgkin lymphoma who received radiation therapy compared to the general population. The authors concluded that the evidence for radiotherapy as a cause for mesothelioma independent of exposure to asbestos is expanding and that the diagnosis of mesothelioma should be considered whenever related symptoms arise in previously irradiated patients.[59]

Li *et al.* (2015) reviewed the extensive experience at Duke University Medical Center involving 3600 patients with malignant mesothelioma and focused on the clinicopathologic features of 45 who had a wide variety hematologic malignancies including lymphomas but also acute and chronic leukemia.[60] Of the patients with Hodgkin lymphoma, 89% had radiation therapy 9 years or more before their diagnosis of mesothelioma. The median interval between radiation therapy for all patients with hematologic malignancies and mesothelioma was 26 years (range 9 to 42 years), an extremely wide range most likely influenced by other host, disease-related, genetic, and environmental factors. Patients with hematologic malignancies treated with therapeutic radiation and who developed mesothelioma tended to be younger, had a longer interval between the diagnosis of a hematologic malignancy and mesothelioma, had a longer survival rate, and were more likely to have epithelioid histology compared with non-irradiated patients. This is not surprising as most mesothelioma patients have epithelioid histology.[61] Given these numerous and recurring findings, it is now generally accepted within the medical community that there is an increased risk of a second cancer for survivors of Hodgkin or non-Hodgkin lymphoma.[62]

While the risk of second cancers, including mesotheliomas, appears strongly associated with prior radiotherapy for HL and NHL, there has been insufficient study to confirm if the same association exists for patients who received therapeutic radiation for other primary cancers, particularly in those cases where radiotherapy was directed to sites distant from the secondary tumor. However, support for the etiologic role of radiation therapy for primary tumors other than HL and NHL in causing mesothelioma does exist. Patients who received radiation therapy for malignancies, such as testicular cancer[63] and Wilms tumor,[64] have developed mesothelioma. In 2007 Travis *et al.* reported on a study of 40,000 survivors of testicular cancer.[65] These researchers observed statistically elevated risks for numerous second cancers including malignant pleural mesothelioma and cancer of the lung.[66] Such findings should not be surprising given that even organs far from the irradiated field are exposed due to scattered radiation, as well as leakage from the radiation source.[67] One must further consider the radiation received from diagnostic medical imaging studies including CT scans, the radioisotope (FDG in a PET or PET/CT scan), bone scans, nuclear cardiac function studies, lumbosacral spine films, and chest x-rays when calculating the total dose of therapeutic radiation administered. For quite some time, oncologists have been justifiably concerned about the additional radiation to which patients are exposed from diagnostic medical imaging studies.[68]

The studies of Farioli *et al.* published in 2013 and 2016 add further support to the point that it is the carcinogenic effects of radiation and not the type or location of the original irradiated tumor that matters. Farioli *et al.* (2013) reported an increased risk of malignant mesothelioma in 571,000 men with prostate cancer treated with EBRT.[69] Despite a radiotherapy field restricted to the pelvic area and abdominal cavity, thirty cases of pleural mesothelioma were observed over 120,731 person-years of follow-up. The risk increased with the number of years since the initial use of EBRT.[70]

The more recent findings of Farioli *et al.* (2016) provide further evidence supporting an association between exposure to EBRT and risk of mesothelioma regardless of the location of the irradiated field. In this study investigators analyzed SEER data from 1973-2012 and evaluated survival models adjusted for age, gender, race, year, surgery, and asbestos exposure. Hazard ratios (HR) were estimated with reference to non-irradiated patients and a distinction was made between scattered and direct irradiation to evaluate dose response. A total of 301 cases of mesothelioma were identified with 265 of them located within the pleura. The study showed that EBRT increased the risk of mesothelioma and calculated a hazard ratio of 1.34. Interestingly, no signs of a dose response were found, suggesting that the risk of mesothelioma is increased regardless of the dose or field of radiation administered.[71]

Parties facing liability for alleged asbestos-induced mesotheliomas are well advised to explore any and all sources of radiation exposure, particularly radiation therapy for HL and NHL, as an alternative to asbestos as the cause of the disease. Although more medical data can be found to support radiotherapy as a cause of mesothelioma when the radiation field is close to the site of the mesothelial tumor, as discussed above, there is a substantial body of medical literature supporting an association, if not causal relationship, between secondary mesotheliomas and more distant radiation fields. Latency periods in radiation-induced mesotheliomas are shorter with a wide range of contributing factors such as the age of the patient, undetermined molecular

genetic factors that influence an individual's ability to repair radiation-induced changes in DNA, other sources of radiation (e.g., medical imaging studies), and immune function.[72] Crucial to advancing this defense is a development of a complete medical history related to the prior irradiation, including specifics as to the timing, duration, dose, and method of the therapy. Clearly, qualified expert witnesses will be necessary with the background and experience needed to advance the defense and survive *Daubert*- or *Frye*- based challenges.

Environmental Exposures

As occupational exposure levels continue to decline in most countries, environmental exposures from mineral fibers other than asbestos and from naturally occurring asbestos (NOA) have been identified as potential alternative causes of mesothelioma and other cancers traditionally linked to occupational asbestos exposure. Studies concerning many of these environmental causes are in the early stages and until further, comprehensive studies are completed, defense counsel will likely face difficulties meeting the threshold requirements for admissibility. While analysis of if, and to what extent, environmental exposures can be linked to mesothelioma and other cancers continues to develop, savvy practitioners should continue to evaluate environmental exposures as a potential, alternative cause, particularly in cases with tenuous occupational exposures.

Erionite

Erionite is a zeolite material found mostly in volcanic regions.[73] Studies first identified erionite as potentially causative of mesothelioma in the late 1970s following a high incidence of mesotheliomas in some villages of Cappadocia, Central Anatolia, Turkey, where the soft volcanic rock was cut to make walls of houses and a whitewash plaster finish.[74] Following mineralogical studies and the analysis of lung tissue, the increased rate of mesotheliomas in this region of Turkey was linked to erionite of inhalable size in the region's bedrock.[75] Later experimental animal studies confirmed the high carcinogenic potential for erionite, with some studies describing it as more carcinogenic than chrysotile and crocidolite in increasing the risk of mesothelioma.[76] Research has also shown that erionite exposures result in pleural and interstitial fibrotic changes, similar to those found with asbestos exposure.[77]

Once believed to be a health risk only in Turkey, erionite deposits have been identified in Italy and North America, including at least 12 U.S. states, with some of the highest concentrations of this fiber found in the Intermountain West of the United States from Oregon into Mexico and the Sierra Madre Occidental region.[78 79] To determine the potential health implications of erionite in the United States, one study compared erionite from the Turkish villages to that from Dunn County, North Dakota where researchers discovered that more than 300 miles of roads — including 32 miles of school bus routes, parking lots, and playgrounds — were surfaced with erionite-containing gravel from the surrounding area.[80] Researchers found that the physical and chemical properties of erionite from Turkey and North Dakota are very similar and showed identical biological activities.[81] Air sampling in North Dakota demonstrated elevated airborne erionite concentrations compared to similar sampling done in Turkey.[82] An increased rate of mesotheliomas in North Dakota has not occurred, which the study's authors attribute to the latency period for mesothelioma and the recency of the increase in intensity, frequency, and duration of potential exposure resulting from increased construction and development in the area.[83] The authors do note that studies on erionite-induced mesotheliomas in the United States are limited, but have recommended the implementation of preventive and early detection programs in the United States, similar to those being implemented in Turkey.[84]

In cases where the possibility of erionite exposure exists by virtue of where the plaintiff has lived throughout his or her life, tissue digestion may be the key to refocusing the discussion as to cause. While the academic exploration of North American erionite exposure as a cause of mesothelioma is still in its early stages, the science on the potency of erionite certainly exists as does the proof that North American erionite is the geologic analog to that from Turkey. Studies linking mesothelioma to erionite exposure in North America do exist and can be referenced in support of the position that a mesothelioma was caused by erionite exposure.

An erionite-associated mesothelioma with pleural plaques and pulmonary fibrosis was first reported in North America in 2009.[85] The case involved a 47 year-old male with a right pleural mesothelioma with metastasis to the lymph nodes. He lived in Mexico for 20 to 25 years, after which he resided in the United States. His history identified possible exposure to asbestos-containing floor tiles for two years in the late 1980s

when he worked in maintenance for a supermarket. A digestion study on the patient's lung tissue contained fibers indicative of erionite. There was no evidence found for commercial amosite, crocidolite, chrysotile, or non-commercial amphiboles.[86] At least one case report has linked a patient's mesothelioma to environmental erionite exposure in Mexico, where the digestion study and fiber composition analysis confirmed the presence of fibers suggestive of erionite and the absence of asbestos.[87] A high incidence of lung cancer and mesothelioma has been linked to erionite exposure in a rural area in Central Mexico.[88]

Fluoro-edenite

After a cluster of mesothelioma cases was detected in Biancavilla, Sicily, an epidemiological study was commenced to identify potential environmental causes, which led to the identification of fluro-edenite as potentially causative.[89] A total of 17 cases of mesothelioma were reported, of which two had possible asbestos exposure and five in which asbestos exposure could not be excluded. A mineralogical study noted that volcanic materials from Mount Etna were widely used in the building industry and for road paving, leading to the identification of the mineral fluoro-edenite. Later animal studies showed a high incidence of peritoneal mesotheliomas and to a lesser extent pleural mesothelioma in animals treated with fibrous fluoro-edenite.[90]

Naturally Occurring Asbestos

The presence of Naturally Occurring Asbestos deposits have been extensively described in the geological literature.[91] Naturally occurring tremolite and/or chrysotile deposits have been discovered in Italy, Bulgaria, Turkey, Greece, Corsica, Cyprus, and New Caledonia, and crocidolite has been described in a rural area of southwestern China.[92] Domestically, the scientific inquiry has been focused on several specific locations including Libby, Montana; Fairfax County, Virginia; and El Dorado Hills, California, among others.[93] Exposures from NOA deposits have been described following soil disturbance from agricultural tilling and road building, as well as recreational activities on unpaved fields and trails.[94]

In response to increased concern related to NOA exposures Pan *et al.* published the first domestic epidemiology study examining a relationship between residential proximity to NOA deposits and mesothelioma risk.[95] The researchers reported a 6.3 percent decrease in the odds of developing pleural mesothelioma[96] for every 10 km which the subjects lived further away from the NOA source.[97] However, various letters to the editor have questioned the methodology of this study.[98] Lui *et al.* have recently published an epidemiological review of the literature concerning environmental exposures and mesothelioma.[99]

Where an epidemiological link between a NOA deposit and mesothelioma risk has not been reported in the literature, ambient air measurements, such as are published by the California Air Resource Board, will be instrumental in making out an alternative causation defense.[100] The intrepid defense counsel may be further guided by the work of Webber *et al.*, who have attempted to reconstruct ambient air concentrations associated with the historical talc mining operations in Gouverneur, New York by analyzing sedimentary cores of lakes and marshland in the vicinity of the NOA deposits.[101] Alternatively, historical ambient exposure levels may be extrapolated by analyzing tree bark and core samples, which have been shown to act as reservoirs for wind-blown fibers, for the presence of asbestos.[102]

Conclusion

As litigants on the defense side of cases involving a diagnosis of mesothelioma, we have likely become stuck in the well-worn, albeit rutted, path of asbestos litigation. Mere acceptance of asbestos as a cause of every mesothelioma, pleural or peritoneal, ignores science or, at a minimum, the plaintiffs' burden of proof. There is no question that asbestos can cause mesothelioma. The questions posed here are what percentage of those cases are not asbestos-related, and how we might present that information at trial. Whether it is genetics, therapeutic radiation, or environmental concerns, significant alternative reasons for the development of some percentage of the mesothelioma-diagnosed population exist.

Whether the question is the existence of a genetic mutation or exposure to radiation, etc., our first step is recognition of the potential issue followed by the necessary investigation to support the claim and expert presentation. There will undoubtedly be court battles as motion practice will likely be necessary to obtain certain information or expand beyond the "typical" discovery done in an asbestos case. Improved deposition questioning will also be key to develop the factual predicate

for these defenses. Lastly, the identification and development of experts to assist in the presentation of these issues will also be a challenge. Regardless of the effort involved, resetting the balance to exclude this group of cases from this litigation and free the defense from this rut is the goal.

Endnotes

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MEALEY'S LITIGATION REPORT: ASBESTOS
edited by Bryan Redding
The Report is produced twice monthly by

1600 John F. Kennedy Blvd., Suite 1655, Philadelphia, PA 19103, USA
Telephone: (215)564-1788 1-800-MEALEYS (1-800-632-5397)
Email: mealeyinfo@lexisnexis.com
Web site: http://www.lexisnexis.com/mealeys
ISSN 0742-4647