Have the Reports on Idiopathic Mesothelioma Reached Critical Mass?

A Survey of the Existing Research in the Context of the Asbestos-Mesothelioma Paradigm

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I. Introduction: The Paradigm

The relationship between occupational asbestos exposure and the perceived increase in the incidences of malignant mesothelioma forms the paradigm through which this rare form of cancer has been studied. The purpose of this paper is to review the existing research supporting the occupational asbestos-malignant mesothelioma paradigm to quantify the growing mass of anomalies reported in that research. As the volume of reports on cases of nonasbestos-malignant mesothelioma continues to grow, and the mechanisms causing that disease become better understood the number and validity of alternative causes for this disease will begin to emerge.

Writing on the philosophy of science, Thomas Kuhn described the development of scientific knowledge in terms of a succession of paradigms. A paradigm is a system of beliefs built upon a foundation of assumptions that have been accepted as absolute truth. These belief systems, or paradigms, once established, will remain unchanged so long as only a limited number of exceptions or "anomalies" challenging the absolute truths are introduced into the body of knowledge. Over time, however, as additional information is processed, as a more detailed understanding of the disease process develops, and as the sheer mass of anomalies grows, they will eventually reach critical mass and either destroy the existing paradigm or force it to change or "shift." In some instances existing paradigms' ability to resist these forces is enhanced by support from sociopolitical interests both within and surrounding the scientific community.

The study of malignant mesothelioma was inexorably linked to the occupational exposure to asbestos with the publication of the studies by Selikoff and others in the 1960s. The overall strength and vitality of this established paradigm is most clearly illustrated by those studies in which the frequency of occurrences of mesothelioma acts as a surrogate measure of the asbestos exposure experienced by a group. *See, e.g.*, De Vos, I.H., Lamont, D.W., Hole, D.J. *et al.*, "Asbestos and Lung Cancer in Glasgow and the West of Scotland," *BMJ* 1993; 306: 1503-6.

Over the lifetime of a paradigm, it can be strengthened and attacked. For example, the studies measuring the accuracy of self-reports of occupational exposure to asbestos strengthened the asbestos-mesothelioma paradigm. By measuring the frequency of those reports against the number of positive pathologic and radiographic tests in the reporting group, researchers were able to establish that a significant number of subjects reporting no asbestos exposure had positive test results. Hirsh, A., Brochard, P., *et al.*, "Features of Asbestos-Exposed and Unexposed Mesothelioma," *Am. J. of Indust. Med.*, 3: 413-422 (1982).

In that study, 36 cases of pleural and peritoneal mesothelioma, in which subjects completed questionnaires documenting smoking habits and known asbestos exposures, were correlated with mineralogical analysis and radiographic studies conducted in 28 cases. The researchers found that all ten individuals who reported heavy occupational exposures to asbestos had positive findings for asbestos exposure based on both mineralogical and radiographic testing. It was also discovered that one female originally included in the "moderate definite group" had actually reported a household exposure exceeding some occupational exposures. In the group of moderate definite exposures all mineralogical analyses were positive while only 80 percent of the subjects exhibited radiological abnormalities. In the group without past exposures, low levels of asbestos were found in two out of six samples tested, while a high level of asbestos was found in lung tissue samples of a third. One member of that group had positive radiological findings without any history of past exposure. Of the nine subjects whose questionnaires were inconclusive, six were found to have some asbestos present in biological samples, with only three instances of corresponding radiological abnormalities.

Ultimately, the results of that study supported the unstated belief that patients were underreporting asbestos exposures. This study fueled speculation that in many patients who did not report known occupational exposures to asbestos, a sufficient amount of asbestos might be found in tissue samples to support the asbestos-mesothelioma connection.

The ability of a paradigm to shift or adjust to accommodate a frequently occurring "anomaly" was demonstrated when the occupational asbestos-mesothelioma paradigm did shift to accommodate the reports of malignant mesotheliomas diagnosed in women. When these females were studied for possible occupational exposure, the investigations revealed that although the women generally did not have an occupational exposure to asbestos, many of them had husbands or fathers who worked in asbestos-related industries. Vianna, N. and Polan, A., "Non-Occupational Exposure to Asbestos and Malignant Mesothelioma in Females," *Lancet,* May 20, 1978: 1061-1063. It was suggested that the high incidence of mesotheliomas in these women could be attributed to their exposure to the asbestos fibers carried home on the clothes of the male asbestos workers.

That study provides an illustration of the adverse effect a paradigm can have on a researcher's desire to explore a novel finding that does not fit within the existing paradigm. In that study, Vianna and Polan reported an "unusually high frequency of cancer among the parents of mesothelioma patients." *Id.*, at 1063. They described this finding as "difficult to interpret," suggesting that it could be indicative of a genetic factor affecting susceptibility to mesothelioma. *Id.*

After the asbestos-mesothelioma paradigm shifted to accommodate mesotheliomas in individuals who were not directly exposed to asbestos, it accommodated a substantial number of reported mesotheliomas falling outside of the scope of the existing paradigm. For example, Brenner, J., Sordillo, P.P., *et al.*, "Malignant Mesothelioma of the Pleura," *Cancer* 49; 2431-2435 (1982), studied a group of 123 mesothelioma patients, out of which only 13 percent had documented occupational exposures to asbestos. They found that 14 members of the group developed mesothelioma after working in industries in which they were exposed to other types of dust and chemicals, one had a history of radiation treatment for another cancer and 12 had histories of prior lung diseases. Despite these findings, the researchers continued to attribute a majority of those mesotheliomas to a probable exposure to asbestos.

The continued vitality of an existing paradigm can be enhanced by external sociopolitical and economic factors. With respect to the asbestos-mesothelioma paradigm, the paradigm has been bolstered by the compensation schemes developed to provide individuals diagnosed with occupationally caused mesothelioma compensation for their injury. Examples of these schemes can be found in both the U.S. and the United Kingdom. While the development of the scheme itself does not support the paradigm, the information disseminated not only to the legal and governmental communities, but shared with the members of the scientific and medical communities can influence the thinking of members of those communities. For example, the British Thoracic Society Standard of Care Committee issued a statement published in *Thorax* 2001; 56:250-265, described the *legal test* that must be satisfied before an individual is eligible for compensation:

> the diagnosis and causation should be established on the *basis of probability*. Hence, *pathological diagnosis is not mandatory* for compensation issues although an unequivocal diagnosis will remove subsequent room for debate. Patients who cannot identify exposure to asbestos are not eligible for compensation.

Id., at 261-262 [emphasis added]. In a similar manner, physicians in the U.S. and other countries are also reminded of the pertinent legal issues to consider when treating patients suffering from mesothelioma. *See, e.g.*, Guidotti and Goldsmith, (1986), *supra.* It can be reasonably argued that the decision to limit the right to recover monetary damages to those individuals with diseases attributed to occupational exposures to asbestos, contributes to the

apathy exhibited by some researchers when confronted with cases of mesothelioma falling outside of the existing paradigm.

As discussed above, an established paradigm can accommodate a limited number of anomalies. For example, a number of "rare" or "idiopathic" mesotheliomas have been accepted within the asbestos-mesothelioma paradigm. *See, e.g.*, Craighead, J.E., *Pathology of Environmental and Occupational Disease,* 468 (St. Louis: Mosby, 1995) (some cases of mesothelioma are "spontaneous occurrences"); British Thoracic Society Standard of Care Committee, "Statement on Malignant Mesothelioma in the United Kingdom," *Thorax,* 56:250-265 (2001) (mesothelioma is rare in subjects without asbestos exposure). The review of the case control studies, published between 1965-1975, linking between 12 percent to 93 percent of mesotheliomas to asbestos exposure, Britton, M., "The Epidemiology of Mesothelioma," *Seminars in Oncology*, 29 (1); 18-25 (2002), provides an excellent example of the ability of the asbestos-mesothelioma paradigm to accommodate evidence that a growing proportion of diagnosed malignant mesotheliomas might not be linked to asbestos exposure.

II. Challenges to the Existing Paradigm

When defendants involved in asbestos litigation attempt to introduce other possible factors causing or contributing to the numbers of diagnosed mesotheliomas, they are confronting an obviously well-established paradigm. That existing paradigm survives intact until the body of anomalous findings reaches sufficient mass to create a high enough level of "discomfort" in believers of that paradigm, to necessitate a reexamination of the paradigm's foundational presumptions. The asbestos-mesothelioma paradigm has demonstrated a surprising amount of elasticity in the face of the growing body of anomalous findings.

The report published by Peterson, J.T., Greenberg, S.D. and Buffler, P.A., "Non-Asbestos-Related Malignant Mesothelioma," *Cancer* 54:951-960 (1984), is an excellent example of the type of report that can challenge an established paradigm. Peterson, *et al.*, reviewed prior reports documenting the total number of mesotheliomas diagnosed in various groups to identify those mesotheliomas in which exposure to asbestos had been found. The number of asbestos-related cases compared to the total cases ranged from as low as four out of 31 cases, (Ratzer and coworkers) to as high as 76 out of 83 cases (Newhouse and Thompson). Based on those findings, the researchers suggested that some other, unidentified, environmental agent could have played a role in increasing numbers of malignant mesotheliomas reported. *See also* Law, M.R., Ward, F.G., *et al.*, "Evidence for Longer Survival of Patients with Pleural Mesothelioma without Asbestos Exposure," *Thorax* 38:744-746 (1983) (focusing of the relationship between either an absence or background exposure to asbestos and survival time).

In general, as the body of anomalous findings continues to grow, an existing paradigm should eventually begin to weaken and allow other flaws in the presumptions supporting its development to emerge. For example, reports have been published documenting the difficulty of making an accurate initial diagnosis of mesothelioma. Shepard, K.E., Oliver, L.C. and Kazemi, H., "Diffuse Malignant Mesothelioma in an Urban Hospital: Clinical Spectrum and Trend in Incidence over Time," *Am. J. Indust. Med.* 16:373-383 (1989). In that study, the researchers described their findings when they looked back in an attempt to verify the accuracy of past diagnoses of mesotheliomas, explaining that the inaccuracies found could be attributed to the extreme variability in the histological appearance of the tumors.

Shepard, *et al.,* started with a group of 75 cases in which definite or equivocal mesotheliomas had been previously diagnosed. They found four primary malignant mesotheliomas, seven benign fibrous mesotheliomas, and 64 cases of diffuse malignant pleural mesothelioma. Of those 64 cases, only 43 were considered definite, on review, based on both the reported evidence of asbestos exposure and the pathologic diagnosis. Of the remaining 21 cases, atypical histological findings were observed in 15 cases. In the six remaining cases, there were other

primary tumors reported that could produce a microscopic or histochemical pattern indistinguishable from diffuse malignant pleural mesothelioma. Common to all 21 of the equivocal cases, was the absence of reported exposure to asbestos, while asbestos exposures were established based on findings of interstitial fibrosis and/or asbestos bodies in the lung tissue samples in three of that group.

The growing body of research includes reports by pathologists on their efforts to identify specific markers that can be used to differentiate malignant mesothelioma from other cancers. *See* Tubbat-Herrera, E.A. and Knowles, K., "Cytology: Screening or Diagnostic Tool?" *Human Pathology*, (29)12;1356-1366 (1998). For example, a number of studies were published suggesting that the monoclonal antibody Ber-EP4 could be used to distinguish pleural mesotheliomas from primary pulmonary adenocarcinomas. Ordonex, N., "Value of the Ber-EP4 Antibody in Differentiating Epithelial Pleural Mesothelioma from Adenocarcinoma," *Anatomic Pathology*, 109;1:85-89 (1998). Ordonex reviewed those earlier studies and compared those results to his own, before concluding that Ber-EP4 was not a reliable indicator to be used for distinguishing between adenocarcinomas and pulmonary mesotheliomas.

The foundation of the existing paradigm has also been challenged by reports of researchers attempting to understand and explain the biology of the mesothelioma tumor and the mechanisms whereby asbestos induces the development of this cancer. Huncharek, M. "Non-Asbestos Related Diffuse Malignant Mesothelioma," *Tumori,* 88:1-9 (2002). In that study, instead of identifying the elusive mechanism whereby asbestos causes mesothelioma, the researchers found a nonasbestos oncogene with the ability to trigger the development of malignant mesothelioma.

III. The Existing Paradigm Continues to Resist the Pressure Being Exerted by Studies Involving Simian Virus 40

Within the asbestos defense community, research into the link between SV40 and malignant mesothelioma provides an ongoing but unrealized hope that an alternative cause of the development of this disease may eventually be accepted.

A. SV40 and Malignant Mesothelioma

Evidence supporting the link between SV40 and the development of malignant mesotheliomas at the cellular or genetic level has been reported by pathologists, virologists, and cellular biologists, and far exceeds the similar evidence supporting asbestos's link to that disease. Despite these mounting reports, the existing asbestos-mesothelioma paradigm continues to pose a daunting obstacle to the acceptance of the SV40-mesothelioma link. Arguably, the lack of willingness of the courts to admit expert testimony describing this link has hampered its ability to gain acceptance.

In 1998, an asbestos manufacturer's attempt to present expert testimony describing the link between SV40 and mesothelioma was rebuffed by a New York state court as outside of the scope of generally accepted beliefs in the scientific community. *In Re Eighth Judicial Dist. Asbestos Litig.,* 1998 N.Y. App. Div. Lexis 14599 (4th Dep't.). New York is one of the remaining jurisdictions in which the admissibility of expert testimony is evaluated under the standard set forth in *Frye v. United States,* 54 App. D.C. 46, 293 F. 1013. Under *Frye, supra,* expert testimony is not admissible unless the relevant scientific community has *generally accepted* the *opinion* the expert intends to offer. In that 1998 case, the New York court excluded the proffered testimony on SV40, based, in part, on a finding "that no reported decision, state or federal, has ruled that the proffered evidence may be admitted." *In Re Eighth Judicial Dist.,* at *8. A recent Lexis search of all states cases, did not reveal any decisions in courts applying the standard set forth in *Daubert v. Merrell Dow Pharmaceuticals Inc.,* 509 U.S. 579, 113 S. Ct. 2786, 125

L. Ed. 2d 469 (1993), to evaluate the admissibility of similar testimony. Unlike *Frye, Daubert* does not require that the proposed testimony be "generally accepted in the relevant community," but provides a greater willingness to consider the admissibility of newer scientific theories or findings.

B. A Brief History of the Development of the SV40-Mesothelioma Link

Before a focused attack on the existing paradigm can be mounted by suggesting a relationship between SV40 and mesothelioma, a brief review of the studies reporting that connection is required. The connection between this virus and cancers was identified at the cellular level, not in studies of large population groups.

In the late 1980s a "quantum boost" occurred in the field of cancer biology. Cancer biologists began studying the relationship between genetic mutations at the cellular level and the development of cancers. Their research led to "the realization that viral proteins from three unrelated DNA tumor viruses had evolved the capacity to transform cells by binding to a set of cellular proteins that included the retinoblastoma (RB) tumor suppressor gene product." Kaye, Frederic J., "The Retinoblastoma-Like Protein Family: Still in the Shadow of the RB Gene?" *J. Nat'l Cancer Inst.*, 90: 1418-1419, at 1418 (1998). According to Kaye, the observation that RB could mediate growth inhibition or promote cellular differentiation both fueled the search for new cancer treatments and raised a controversial question about the role of DNA tumor viruses in human disease.

In 1995, a study of human malignant mesothelioma tumors that were examined for gene mutations was published. Researchers had been examining tumor cells to determine whether the particular genetic sequences found in the ras gene, a common human oncogene, could be found in mesothelioma cells. They did not find H-ras mutations in any of the 11 mesothelioma tumors studied. Of those 11 mesothelioma tumors, only three were identified as being related to asbestos exposure. However, in seven of the eight nonasbestos-related tumors, SV40 DNA was found. It was also found in one of the asbestos-related tumors. The researchers also observed changes in p21 (a suspected tumor suppressor) in two of the nonasbestos tumors. Cristaudo, A., Vivaldi, A., *et al.*, "Molecular Biology Studies on Mesothelioma Tumor Samples: Preliminary Data on H-Ras, P21, and SV40," *J. Envtl. Pathology, Toxicology & Oncology* 14(1):29-34 (1995).

C. The Evidence Supporting a Link between SV40 and Mesothelioma Continues to Mount

Within months of the publication of Kaye's study, Janet Butel and John Lednicky published their report, "Cell and Molecular Biology of Simian Virus 40: Implications for Human Infections and Disease," *J. Nat'l Cancer Inst.*, 91:119-134 (1999). They described SV40's prior role as a contaminant in polio vaccines distributed between 1955 through early 1963 and described the process whereby the virus became a favored laboratory model for the study of molecular processes and cellular transformations. The use of SV40 virus in those studies confirmed the virus's ability, as a DNA tumor virus, to induce rodent tumors and transform a wide variety of cells in culture, including human cells. Butel and Lednicky also reported that the viral replication protein, named large T antigen, or Tag, had been identified as a viral oncoprotein. It was eventually determined that, while SV40 in monkeys was generally benign, the virus could become pathogenic in immunocompromised animals and was capable of infecting multiple tissues.

Butel and Lednicky reported SV40 infected humans associated with certain types of human tumors. Following on the heels of the research conducted in the early 1980s into HIV, the notion that a simian disease could infect humans no longer seemed "incomprehensible." SV40's role in human health was studied for a relatively brief period of time after its discovery in the polio vaccine. Those studies included a 17-19 year study of newborns that had been inoculated with the vaccine. No excess risk of mortality was observed in those studies. However, in a

different study of mothers vaccinated for polio during their pregnancies, researchers observed a more than twofold increase in their offsprings' rate of cancer.

According to Butel and Lednicky, the discovery of SV40 DNA in human tumors had been first reported in 1979. Since that time, SV40 DNA and Tag have been found in a wide variety of human tumors, including but not limited to brain tumors, melanomas, meningiomas, mesotheliomas, and others. Further study enabled researchers to distinguish between a variety of the SV40 sequences found in human tumors, leading to the suspicion that the virus entered the human population on multiple occasions, or that the polio vaccines had been contaminated by more than one strain of SV40. The detection of Tag in mesothelioma tumor cells suggested that Tag could be functioning to "dysregulate" growth control pathways in human cells in a manner similar to that described in the study of rodent tumors. At the time the 1999 study was published, it was believed but not established that SV40 infection either caused the development of human cancers or interacted with other cofactors, such as asbestos, to increase a risk of cancer.

In 2000, *Anticancer Research* published a study "confirming" the link between SV40 and mesothelioma. Carbone, M., Rizzo, P., and Pass, H., "Simian Virus 40: The Link with Human Malignant Mesothelioma Is Well Established," *Anticancer Research* 20:875-876 (2000). In that study, the researchers challenged the asbestos-mesothelioma paradigm with the observation that asbestos did not transform human mesothelioma cells in tissue cultures, while SV40 had been found to preferentially cause mesotheliomas in hamsters and was present in up to 80 percent of the human mesotheliomas in the U.S. According to these writers, SV40 Tag was found to bind and inactivate a number of cellular tumor suppressors, thereby inducing a large number of chromosomal aberrations in SV40 infected cells.

In that study it was also reported that SV40 could not be found in tumors from Finnish or Turkish patients. However, the absence of the virus was explained when researchers found that contaminated polio vaccines had not been sent to either Finland or Turkey between 1955 through 1963.

In a related study, laboratory error was eliminated as a possible cause for the failure to find SV40 in Finnish mesotheliomas. Testa, J.R., Carbone, M. *et al.*, "A Multi-Institutional Study Confirms the Presence and Expression of Simian Virus 40 in Human Malignant Mesotheliomas," *Cancer Research*, 58; 4505-4509 (1998). Four independent laboratories were selected to participate in the study. One of those four was the Finnish lab that had failed to detect SV40 in the Finnish mesotheliomas. Each lab analyzed tissue samples taken from the same mesothelioma specimens that had been prepared and processed in the same manner. The results obtained were generally consistent.

In addition to conducting two separate tests for the presence of SV40 Tag, or SV40 DNA, lung tissue samples from seven of the 12 cases were studied to evaluate the amount of asbestos exposure sustained by each patient. In sum, ten out of 12 mesotheliomas were positive for Tag cells and nine of those ten tested positive for SV40 DNA. Because the two remaining samples tested inconsistently for SV40 DNA and negative for Tag, they were classified as negative. In the two instances in which there was no past history of asbestos exposure and no asbestos fibers found in lung tissue samples, both samples were positive for SV40. In four other lung tissue samples, the number of fibers found was consistent with a background exposure to asbestos, while in the remaining sample in which asbestos fibers were detected, they were present in levels consistent with a low level occupational exposure.

The increase in the number of individuals who develop mesothelioma in which only a low level of asbestos exposure was established spurred further research into the relationship between SV40 and mesothelioma. Rizzo, P., Bocchetta, M. *et al.*, "SV 40 and the Pathogenesis of Mesothelioma," *Cancer Biology* 11: 63-71 (2001), distinguished asbestos, claiming that it is not a mutagenic under a classic model, because while 80 percent of

mesotheliomas were thought to develop in individuals with higher than background levels of asbestos exposure, only five percent of all individuals heavily exposed to asbestos developed mesothelioma.

At the same time, the researchers noted that an estimated *98 million people* in the U.S. received polio vaccines between 1955 and 1963. During that time, it is estimated that one-third of the vaccines administered were contaminated with SV40. The researchers also recognized that it was possible that the virus spread by means other than injection. Over time, more than 26 research groups have confirmed the presence of SV40 in human mesotheliomas or other tumors. Mesothelial cells reacted differently than other cell types to SV40. In fact, it has been suggested that mesothelial cells and SV40 live in a sort of parasitic relationship. While asbestos alone cannot transform human cells in vitro, asbestos combined with SV40 has shown some cocarcinogenicity. In fact, according to some, it is speculated that asbestos acts as an immunosuppressant that allows SV40 infected cells to escape immune detection.

D. SV40 Becomes an Accepted Cause of Mesothelioma but the Asbestos-Mesothelioma Paradigm Survives

This year, *Thorax* published another article "confirming" the connection between SV40 and pleural mesothelioma. Baldi, A., Groeger, A.M., *et al.*, "Expression of p21 in SV40 Large T Antigen Positive Pleural Mesothelioma Relationship with Survival," *Thorax*, 57:353-356 (2002). This report begins with a reminder that while the relationship between asbestos exposure and mesothelioma is generally accepted, the mechanism whereby asbestos induces mesothelioma remains unknown. Twenty-nine malignant mesothelioma specimens were initially selected for this study, but two were excluded because they were obtained from subjects who died of causes other than mesothelioma. A history of asbestos exposure was identified for only three samples, but *all 29* samples tested positive for the presence of SV40.

In that study, researchers found that the p21 protein was expressed in both normal and neoplastic tissue. The researchers described p21 as a "downstream target of p53," the protein typically involved in the mutation of mesothelial cells affected by SV40 Tag. A positive relationship between the level of p21 and the overall survival of the patients was observed. When less p21 was found, it appeared that the tumor appeared more aggressive and adversely affected the prognosis of the patient.

IV. Identification of Other Factors Relating to the Development of Malignant Mesothelioma Has Not Forced the Existing Paradigm to Shift

As demonstrated above, the body of research supporting the link between malignant mesothelioma and SV40 continues to grow. The biological mechanisms occurring following infection with SV40 have been identified and confirmed in multiple studies. The relevant time period over which SV40 contaminated polio vaccines were widely distributed further supports the perceived growth of the number of patients diagnosed each year with asbestos related mesothelioma, despite the presumption that the concentration of fibers involved in occupational exposures decreased over time. The evidence of the relationship between asbestos exposure and mesothelioma remains primarily in the realm of the epidemiologists, while the biology of the relationship remains poorly understood. Huncharek, M., "Non-asbestos Related Diffuse Malignant Mesothelioma," *Tumori,* 88:1-9 (2002).

Huncharek attempted to rationalize the growing number of reports of mesotheliomas diagnosed in an absence of asbestos exposure to the possible underreporting of the exposure. He also suggests that there may be a "background" incidence of nonasbestos mesothelioma, evidenced by the incidences of the disease in women. While holding fast to the existing asbestos-mesothelioma paradigm, Huncharek identified some other possible causes for mesothelioma, including exposure to high doses of radiation. Although he briefly described the various

reports linking mesothelioma to high therapeutic doses of radiation, Huncharek dismissed this relationship as a possible chance occurrence, describing the studies as "anecdotal."

A. Radiation Exposure and Mesothelioma

Huncharek suggested that there could be some relationship between exposure to radiation and mesothelioma, and traced that back to early animal experiments. After describing reports of human mesothelioma linked to radiation treatment, he dismissed most of those reports as anecdotal, and specifically denied any relationship between treatment for Hodgkins disease and mesothelioma. However, Huncharek failed to consider a 1982 report of an incident of malignant mesothelioma in a patient who had been treated seven years earlier with radiation therapy to the chest for Hodgkin's disease. Brenner, J., Sordillo, P.P., *et al.*, "Malignant Mesothelioma of the Pleura," *Cancer* 49:2431-2435 (1982).

Huncharek also failed to credit a report on five cases of mesothelioma related to radiation therapy. Antman, K.H., Corson, J.M, *et al.*, "Malignant Mesothelioma Following Radiation Exposure," *J. Clinical Oncology*, 1(11): 695-700(1983). In that article the medical histories of four patients without known occupational exposures to asbestos were described. In one case, however, it was reported that the patient was a geology professor who had worked in caves and was an avid spelunker. Each patient had been treated with radiation therapy years before they developed mesothelioma. The researchers pointed out that patients with prior histories of cancer are not typical of the population of mesothelioma patients. In three of the cases, the radiation had been used to treat other cancers, while the fourth patient had received radiation to prevent scarring after a thyroidectomy. *See also* Peterson, J.T., Greenberg, S.D., and Buffler, P.A., (1985), *supra,* a survey including summaries of seven prior reports on patients who developed mesothelioma following radiation therapy, absent a reported history of asbestos exposure; and, Anderson, K.A., Hurley, W.C., *et al.*, "Malignant Pleural Mesothelioma Following Radiation in a 16 Year Old Boy," *Cancer* 56: 273-276 (1985), reported on a single case in which a patient with a past history of radiation and chemotherapy for Wilms' tumor, including additional radiation treatment for metastasis pulmonary disease, subsequently developed malignant pleural mesothelioma, absent a past history of asbestos exposure.

Another very similar case, was reported by Austin, M.B., Fechner, R.E. and Roggli, V.L., "Pleural Mesothelioma Following Wilms' Tumor," *Am. J. Clinical Pathology*, 86: 227-230 (1986). That subject was a 28-year-old woman with a left pleural mesothelioma and a past medical history positive for a left nephrectomy for Wilms' tumor followed by radiation therapy. She also was treated with radiation to the right lung for a presumed metastatic tumor. Lung tissue samples were examined and a "normal range" of asbestos fibers was found in that tissue.

The researchers summarized prior reports on the development of mesothelioma in former Wilms' tumor patients. They reported that out of 14,610 patients treated for childhood cancers, 1,451 were Wilms' tumors. Twenty-one of those patients developed a second malignant neoplasm. In one study of 260 survivors of Wilms' tumors, seven were reported with malignant second tumors, but none were malignant mesotheliomas. In another study of 487 cases of Wilms' tumor, eleven cases developed second cancers, one of which was a pleural mesothelioma. In three other cases of pleural malignant mesothelioma developed following radiation therapy for Wilms tumor, only one occurred on the same side as the patient's nephrectomy. Accordingly, the relationship between the treatment for Wilms' tumor and malignant mesothelioma was more likely explained by hereditary disposition rather than the radiation treatment received.

In 1988, Huncharek, *et al.*, reported on a case of pleural mesothelioma in a nuclear engineer. This patient had adamantly denied ever being occupationally exposed to asbestos, but researchers discredited his report, accepting the reports of coworkers. The patient was employed for 27 years as a research nuclear engineer engaged in the design and development of nuclear reactors used in sodium cooled atomic power stations. The patient's

coworkers were questioned about the conditions encountered in the proximity of the sodium cooled power stations. One responded by describing his activities sawing asbestos insulation used on the sodium cooled test reactors, and reported that the research engineers were often present in the area while this work was being done. Other coworkers described the areas in the plants as dusty and filled with asbestos. Huncharek, M., Smith, K., Milatou, R., "Malignant Pleural Mesothelioma in a Nuclear Engineer," *British J. Indust. Med.* ,45:498-499 (1985). Huncharek chose to credit the reports of coworkers, but did not identify the occupations or trades of those workers and failed to report on any findings of fibers in lung tissue samples, if those samples were studied.

Hoffman, J., Mintzer, D., and Warhol, M.J., "Malignant Mesothelioma Following Radiation Therapy," *Am. J. Med.* 97:379-392 (1994), reported on a case of malignant mesothelioma in a case of a patient with a past medical history of Hodgkin's disease, who was treated with radiation therapy nine years earlier. There had been numerous reports on the development of secondary neoplasms after therapy existed and that radiation had been recognized as an etiologic factor.

In 1997, Roggli, V.L, Oury, T.D., and Moffat, E.J., reported on "Malignant Mesothelioma in Women," *Anatomic Pathology,* 1997. They reported the findings that came out of a study of 62 women included in a group of 770 patients with malignant mesothelioma. Fifty-three of the women were diagnosed with pleural tumors, while nine suffered from peritoneal tumors. Five of the women's' medical histories included prior radiation treatment. One woman, whose lung tissue was found to have only a background level of asbestos fibers, had received treatment for Wilms' tumor. There was another woman in the group who had been treated with both radiation and chemotherapy for a prior lymphoma. She had been married to an asbestos-exposed individual. Another wife of an asbestos worker was also treated with radiation and chemotherapy for breast cancer. In her case, tissue samples revealed an increased level of asbestos fibers. Another patient was treated for breast cancer with only radiation therapy, and developed pleural mesothelioma on the same side as her prior treatment. The fifth woman was diagnosed with peritoneal mesothelioma 50 years after being treated with pelvic radiation. There were no pleural plaques or asbestosis found in any of these five women.

Exposure to high levels of radiation provided a defense to the link between asbestos and mesothelioma. *Holbrook v. Lykes Bros. SS Co.,* 80 F.3d 777 (3d Cir. 1996). In that case, defendants suggested that the plaintiff's exposure to high levels of radiation caused his mesothelioma, while working aboard ship in the Pacific Ocean when testing of atomic bombs was being conducted. In that decision, the Third Circuit remanded that case, not because of the defendant's expert testimony in support of this theory, but because the trial court improperly excluded testimony from plaintiff's expert. On retrial, the defense was upheld by the Third Circuit.

B. The Relationship between Genetic Predisposition and Mesothelioma

Huncharek (2002), *supra*, did acknowledge that a familial or genetic predisposition to mesothelioma could exist, and relied to a large extent on the information reported in his 1996 article, Huncharek, M., Kelsey, *et al.,* "Parental Cancer and Genetic Predisposition in Malignant Pleural Mesothelioma: a Case Control Study," *Cancer Letters* 102: 205-208 (1996), for support. In the 1995 study, he reported that 71 percent of the mesothelioma patients studied had at least one parent with a past medical history of some form of cancer, and that this percentage was significantly higher than those in the control group who reported a parent with a past history of cancer. Additional support for the existence of a genetic predisposition to developing certain cancers can be found in a number of other studies identified by Huncharek (2002).

The relationship between a genetic predisposition to mesothelioma was also considered in studies of the high incidences of malignant mesothelioma in the population of Karain and Tuzkoy, two villages located in Central Turkey. In those villages, malignant mesothelioma is responsible for 50 percent of deaths in men and women.

Although the presence of eronite, a mineral used in the construction of homes that has been found to be even more carcinogenic than asbestos in rats, is present in those villages, the genetic relationship between the high incidences of mesothelioma has not been excluded.

C. Incidences of Mesotheliomas in Children Weigh against the Asbestos-Mesothelioma Paradigm

Even Huncharek (2002), *supra,* admits that the occurrence of mesothelioma in children is perplexing. It is difficult to rationalize the long latency period attributed to asbestos-related mesotheliomas to the early deaths of young individuals. Huncharek questioned the accuracy of many of these diagnoses and pointed to the later development of brain metastases in an effort to differentiate some of the other reported cases.

Wasserman, M. and Wasserman, D., "Mesothelioma in Children," *IARC Sci Pub* 30(92); 253-257 (1980), reported on four of the childhood mesotheliomas listed in the Israel Cancer Registry between 1960 and 1974. After acknowledging that the typically long latency was not evident in these cases, they suggested that the children may have been exposed to asbestos fiber in utero. They attributed the truncated latency periods to this unique stage of exposure.

Brenner, J., Sordillo, P.P., and Magill, G.B., "Malignant Mesothelioma in Children: Report of Seven Cases and Review of the Literature," *Med. & Pediatric Oncology,* 9:367-373 (1981), reported on seven childhood cases of mesotheliomas in patients ranging from five years to 17 years old. The study did not propose any cause for these cases, but simply reported on the unusual features found. In six of those cases the cancers spread to other organs. The most unusual of those cases was a 16-year-old girl who was diagnosed with mesothelioma with involvement of the hilar lymph nodes, based on histological review. She was treated with aggressive chemotherapy, and later had a large mass involving the lingual extending into the pericardium surgically removed. Pathologic examination of the tissue from that mass revealed only densely sclerotic areas with chronic inflammatory reaction and no viable tumor cells. According to the authors she remained disease-free for 5.5 years postdiagnosis.

V. When Considered As a Group, the Individual Cases of Reported Mesotheliomas That Were Not Related to Asbestos Exposure Become Increasingly Significant

Considering each of these unusual presentations as unique or idiopathic, without making any effort to find common factors running throughout, diminishes their importance in the evolving landscape of the asbestos-mesothelioma paradigm. When considered these case studies begin to develop critical mass. Accordingly, those reports identifying factors that are believed to cause malignant mesothelioma outside of the existing paradigm, are worthy of careful review and consideration. When researchers have chosen to consider these studies as a group, the results are often impressive.

For example, in one of a pair of reports published in 1991, researchers considered findings in both animals and humans to support the proposition that mesothelioma can be caused by factors other than exposure to asbestos. Ilgren, E.B., and Wagner, J.C., "Background Incidence of Mesothelioma: Animal and Human Evidence," *Regulatory Toxicology & Pharmacology* 13: 133-149 (1991). The authors began their report with a listing of spontaneous mesotheliomas found in animals in nonexperimental settings, reporting that bass, trout, wild rats, mastomys, hamsters, domestic and wild dogs, leopards, elands and cows had been diagnosed with malignant mesotheliomas.

Those researchers also reported on cases of "spontaneous" human mesotheliomas in which there was no history of asbestos exposure. While many of those cases had previously been reported by other researchers as

examples of "anomalous" findings, they had not considered beyond that role. When collected and reviewed, this group of cases revealed that the incidence rate of these spontaneous occurrences ranged from five to 99 percent depending on a variety of factors including, "sex, series size, fiber type and industrial process," and therefore, supported the belief that there was a "possible role of other agents" in the development of malignant mesotheliomas. The researchers also identified various trades in which occupational exposures to substances other than asbestos had been suggested as causing mesothelioma. Those trades included employees working in petrochemical or oil refining plants, stonecutters, leather workers, textile workers, individuals who had occupational contact with copper, nickel, rubber, glass dust or beryllium.

There are a number of other studies identifying factors believed to contribute to the development of mesotheliomas that do not fit within the existing paradigm. For example, Roviaro, G.C., Sartori, F. *et al.*, "The Association of Pleural Mesothelioma and Tuberculosis," *Am. Rev. Respiratory Diseases*,126:569-57 (1982), reported on three patients previously treated for tuberculosis who subsequently developed pleural mesotheliomas. None of the three patients ever worked with asbestos or lived in areas in which there was a high concentration of asbestos. The researchers suggested that under a "chronic stimulation theory," because both asbestos and tuberculosis could cause calcification, it was reasonable to presume that tuberculosis caused pleural mesothelioma. *See also* Hillerdal, G. and Berg, J., "Malignant Mesothelioma Secondary to Chronic Inflammation and Old Scars," *Cancer* 55: 1968-1972 (1985) (two women with past histories of tuberculosis diagnosed with mesotheliomas).

Two cases of pleural mesothelioma were also found in patients with prior histories of chest trauma. In the first case, a 40-year-old female sought treatment for chest pain attributed to a trauma four weeks earlier. Chest x-rays demonstrated an increased density in the right lower chest, and a pleural biopsy lead to the diagnosis of malignant mesothelioma. In the second case, a 77-year-old man sought treatment for complaints of left sided chest pain. He reported having fallen twice in the three weeks prior to seeking treatment. He had a past medical history that included diabetes mellitus, hypertension and coronary artery disease. In his case, a chest x-ray revealed left pleural thickening and an open pleural biopsy revealed malignant mesothelioma. No cause was suggested for either mesothelioma.

VI. Conclusion

It is estimated that there are more than 2,000 cases of mesothelioma diagnosed in the United States each year. Boylan, A., "Mesothelioma: New Concepts in Diagnosis and Management," *Current Opinion in Pulmonary Med.*, 6:157-163 (2000). Although asbestos exposure is the most frequently recognized cause of mesothelioma, approximately 20 percent of all mesotheliomas are not related to asbestos exposure. Baldi, A., Groeger, A.M. *et al.*, "Expression of p21 in SV40 Large T antigen Positive Human Pleural Mesothelioma: Relationship with Survival," *Thorax*, 57: 353-356 (2002).

As demonstrated by the rejection of expert testimony on SV40 in the New York case, it is suggested that the introduction of a new causal theory for mesothelioma be attempted only if the following criteria can be satisfied:

1) Consideration has to be given to the standard applied in the forum of the case for evaluating the admissibility of expert testimony.
2) The history of asbestos exposure should be highly suspect, lung tissue samples should test negative for asbestos fibers and x-rays should be negative for pleural plaques.
3) Tumor tissue samples should be tested and found positive for the theory being introduced. For example, in a situation in which defendants are attempting to introduce the

possibility that a plaintiff's mesothelioma can be attributed to SV40, the tumor tissue tests should corroborate that theory.

4) Medical history corroborating the alternative theory should be sought. Ideally, if the defendants are attempting to implicate SV40, medical records recording the date of plaintiff's polio inoculation as falling in the relevant period are preferred.

5) The appropriate experts should be called to testify within the areas of their expertise. Initially, the courts may be less willing to allow, for example, a virologist to testify as to the mechanisms causing cancers. A team approach may be needed to gain acceptance of the new theory.

The evidence on the cellular and genetic level will continue to challenge the asbestos-mesothelioma paradigm. While epidemiological evidence has typically been found persuasive, the mounting evidence supporting alternative causes is no less persuasive. The incidences of idiopathic or anomalous mesothelioma have always existed. With a growing base of knowledge and improved technologies, the opportunities to exploit that evidence will present themselves to aggressive defendants, and should be exploited in a systematic manner. Recognition of the barrier presented by the existing asbestos-mesothelioma paradigm can only serve to enable those seeking to attack that paradigm.

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