Current Controversies Regarding the Role of Asbestos Exposure in the Causation of Malignant Mesothelioma: The Need for an Evidence-Based Approach to Develop Medicolegal Guidelines

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Asbestos is a group of fibrous silicate minerals that includes two mineralogic groups: amphiboles and serpentines. While the carcinogenic role of amphiboles (eg, crocidolite and amosite) is well established, medical "experts" that tend to strongly advocate their views currently argue in medicolegal cases multiple specific issues regarding the carcinogenicity of asbestos fibers. For example, it is controversial whether chrysotile causes malignant mesothelioma (MM); what are the specific carcinogenic thresholds for amphiboles and chrysotile; what occupations are truly at risk to develop MM as a result of asbestos exposure; what is the role of chrysotile in the development of peritoneal MM; how to assign causation in individuals exposed to multiple industrial products containing variable concentrations of various asbestos fibers; and, what criteria should be used to accept causation in household exposure cases and others. The causation criteria currently acceptable in U.S. courts are surprisingly flexible and subject to variable interpretation by medical "experts." At a time where thousands of individuals are claiming causation of MM by asbestos exposure, there is a need to develop more specific causation guidelines based on scientific evidence. Evidence-based medicine has been proposed as a new approach to the study, teaching, and the practice of medicine and has been used as a process of systematically reviewing the relevant studies in the literature to assess their scientific validity and development of guidelines. This article summarizes some of the current controversies regarding the role of asbestos exposure in the causation of MM and suggests the need for future evidence-based medicine-type studies to develop causation guidelines that could be used consistently during litigation.
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ASBESTOS is the generic name for a group of fibrous silicate minerals that share certain physical characteristics that give them value for various industrial applications.[1-15] Those include heat resistance, tensile strength, resistance to acid and alkali, selective resistance to seawater, and others attributes. Asbestos has been classified into two mineralogic groups: serpentine and amphiboles.[16-22] Chrysotile ("white" asbestos) is the form of serpentine asbestos used in industrial applications. Amphiboles include crocidolite ("blue" asbestos), amosite ("brown" asbestos), and tremolite ("green" asbestos). Actinolite and anthophyllite are still other amphiboles that have not been used frequently in industrial applications.[23-33]

Exposure to amphiboles is the most well-recognized cause of malignant mesothelioma (MM).[34-43] Approximately 60% to 80% of MM in males and 5% to 60% in females are attributable to exposures above background levels (ie, seen in the general population) to fiber types in that group.[33,44,45] However, such data have been extrapolated to the point where many medicolegal "experts" frequently attribute the causation of MM to virtually any amount and any type of alleged asbestos exposure.

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That view is clearly an extreme one. Several well-constructed epidemiologic and pathologic studies have concluded that the carcinogenic role of chrysotile (the mineral that accounts for most commercial asbestos use in the United States) remains highly controversial. Also, analysis of population data has shown that a background level of pulmonary asbestos deposition does exist in the population at large, and therefore attribution of MM requires that tissue concentrations of asbestos must be significantly higher than that level in any given case. Scientific inquiries indicate that chrysotile is either a weak carcinogen that causes pleural MM itself only after very high tissue levels have been accrued, or as a bystander to amphibole exposure (eg, tremolite).[35-37,46-62] Other unsettled issues relating to the causation of MM by asbestos include determinations of threshold levels for carcinogenesis by various fiber types; which occupations are currently at measurable risk for development of MM as a result of asbestos exposure; whether apportionment of causation can be made among various manufacturers in patients with MM whose lungs contain mixed asbestos types; what medical data are necessary to confirm verbal allegations of exposure to asbestos, and others.

There is a real need for the development of specific guidelines that are based on *objective scientific evidence*, regarding various aspects of the causal linkage between MM and asbestos. They could and should be used in courts of law to counter the biases that have been introduced by some medicolegal "experts" and legal advocates, to ensure that legal determinations are based on reproducible and verifiable data as much as possible.

What is Causation in a Court of Law?–Anecdotal Associations Versus Scientific Evidence

The "evidence' linking asbestos exposure to the causation of MM ranges from personal communications and published anecdotal reports of clinicoradiologic findings in small numbers of patients allegedly exposed to asbestos to large epidemiologic or pathologic studies of thousands of individuals exposed to asbestos compared with properly matched controls. Because there has still been insufficient scientific research to definitively determine minimal requirements for causation by particular carcinogens, plaintiffs and defense medicolegal "experts" are given license to select the evidence that supports their subjective beliefs. The United States Supreme Court, in Daubert *v* Merrill-Dow Pharmaceuticals, concluded that an "expert" needs to provide relevant and reliable scientific opinion based on methods and techniques that are generally used in the scientific community and/or rely on peer-reviewed publications for the "testability" of opinions.[63] The "expert" does not need to provide scientific "certainty," but a "51% probability" ("more likely than not"; "within medical probability") regarding the causation of any given disease by any given agent. This general standard is highly subjective–certainly more so than would be allowed in any medical discourse–and it allows "experts" to estimate "probability levels" very imprecisely. For example, some physician-participants in asbestos litigation have stated that any level of asbestos exposure can cause MM, basing that statement on anecdotal reports of patients that putatively developed the disease following minimal household exposure, without regard to fiber type.[64-74] However, it remains highly controversial whether exposure to chrysotile causes MM, and if so, under which circumstances.[34-36]

Attribution becomes even more perplexing in instances where individuals with MM have tissue asbestos burdens representing different fiber types, and they have worked with various asbestos products with dissimilar concentrations of amphiboles and/or chrysotile. In these cases it is unclear whether only selected asbestos fibers contributed to the genesis of MM, or whether there was a synergism in that regard between different fiber types. Paradoxically, in the absence of established science pertaining to those issues, liability is usually assessed using the adage "everybody is liable."

Scientific Methods to Define Causation–Bradford Hill Criteria

Sir Bradford Hill, a British scientist, suggested nine criteria (listed in Table 1) that he believed were needed to establish a causal relationship between exposure to a potential carcinogen and any given neoplasm.[75] The following discussion represents a limited description of how selected Bradford Hill criteria can be applied to the determination of possible causation of MM by asbestos.

Strength of Association

Several well-designed epidemiologic studies have reported up to 19-fold increases in the proportion-

Table 1. The Bradford-Hill Criteria for Causation

Consistency and unbiasedness of findings
Strength of association
Temporal sequence
Biological gradient (dose-response relationship)
Specificity
Coherence of biological background and previous knowledge
Biological plausability
Reasoning by analogy
Experimental evidence

ate mortality rates of workers in certain occupations who were exposed to crocidolite and amosite.[34-37,39,40,76-81] The carcinogenicity of these fibers is felt to be dependent on the dose of exposure(s), the duration thereof, the type of asbestos, fiber size, and other variables. For example, meta-analyses by Hodgson and associates concluded that the relative carcinogenicity of crocidolite, amosite, and chrysotile was 500:100:1, respectively, vis-a-vis MM.[82-85] Several studies by McDonald et al and others have suggested that most MMs seen in workers who are exposed to "pure" chrysotile can be explained by the contamination of those products by tremolite, with or without other amphiboles.[35-37,46-52,86,87]

Temporal Sequence–Latency Period

Most patients develop MM many years after occupational-level asbestos exposure (the so-called "latency period"). For example, a review of over 1,000 cases by Lanphear and Buncher[88] showed that 99% of asbestos-related MM cases were associated with latency periods of $\geq$ 15 years. The length of the latency period in any given case is thought to depend on the dose of asbestos in the early exposures; MM tend to develop after longer periods in persons who are exposed to relatively low doses in the occupational range.[89-94] A minimum of 10 years must elapse after the first exposure to consider an asbestos-related causation for MM.[95]

Biological Gradient: Dose-Response Relationship

Several techniques have been developed for the detection and quantitation of asbestos fibers in tissue and air.[24,33,68,96-121] The results of fiber burden analysis with those methods vary widely between different laboratories. Accordingly, fiber concentrations (eg, the number of fibers per gram of wet or dry lung tissue) in individual samples must be compared with background levels in age- and sex-matched controls that are specific to that laboratory.[115-118] Several studies have shown irrefutably that a dose-response relationship does exist for exposure to amphiboles and the risk of MM. However, it is much more controversial whether this response is linear; indeed, the existence of bimodality in tissue fiber burden values in MM cases.[99,101] would suggest that nonlinearity is likely. Although thresholds of exposure emerge from population studies on asbestos-related MM, methods to determine precise thresholds for individuals have not yet been developed.[122-125]

Biological Plausability–Experimental Models of Malignant Mesothelioma

Asbestos-related neoplasms have been produced experimentally in rats and other animals.[126-129] Technically, these studies confirm the "biological plausibility" of a carcinogenic potential for both amphiboles and chrysotile, but they cannot be extrapolated to provide parallel explanations for the pathogenesis of human tumors. A detailed discussion of this issue is beyond the scope of this review. In general, experimental models have used much higher doses of asbestos than would ever be encountered in humans with MM who were exposed to asbestos; moreover, the length of exposure in experimental models is shorter than in humans, and fibers are usually introduced by artificial routes (eg, intrapleural or intraperitoneal injection) rather than by inhalation.

The Helsinki "Criteria" for the Diagnosis & Attribution of Asbestosis and Pleuropulmonary Malignancies

A group of persons with a professional interest in asbestos-associated diseases met in Helsinki, Finland in the winter of 1997 to develop a report on the diagnosis and attribution of asbestosis and asbestos-related neoplasms.[95] This was the first organized multidisciplinary effort at developing guidelines for causation and drawing information from the literature regarding the pathogenesis of asbestosis, lung cancer, and MM. Unfortunately, the summary of "criteria" proposed by this group provides only very general and internally contradictory answers to many of the specific questions regarding the pathogenesis of MM that are currently being posed in the courts. For example, the document

begins promisingly by outlining objective scientific criteria that can be sought to link pleuropulmonary diseases to asbestos in a causative fashion, but it does not specifically define "low-level asbestos exposure," and indicates that a "careful occupational and environmental history" is sufficient to assign causation. Many epidemiologists would likely contest the latter statement. It clearly does not take into account the considerable variability in carcinogenicity between amphiboles and chrysotile (as much as 500:1) or other issues relating to the vagaries of verbal accounts by patients.

Guidelines From Scientific Studies: Evidence-Based Medicine

Pathologists and other health care professionals are currently challenged by a rapidly growing amount of technical and scientific information. It is often difficult to make informed decisions that require the critical review of multiple studies reporting controversial results. This problem was recognized in the early 1970s by, among others, Dr Archie Cochrane, a British epidemiologist who suggested the need for a systematic review of randomized controlled trials.[130,131] The Cochrane Center was opened in Oxford, England in the early 1990s to foster the development of collaborative systematic reviews of randomized controlled trials across all areas of health care. Evidence-based medicine (EBM) was proposed as a new approach to medical teaching, and it has been defined as "the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions."[132-136] Proponents of EBM believe that complex clinical problems can be addressed via specific, well-formulated questions, followed by a systematic review of relevant studies in the literature, assessment of the quality of the studies, collection of data, analysis, presentation and interpretation of results, and application of these data to improve the quality of medical practice.[132-134,137] A detailed description of EBM methodology is beyond the scope of this discussion, but it includes the use of systematic reviews, evidentiary synthesis, integrative review, meta-analysis, and other statistical methods. A synopsis of these issues is available on the Internet (http://www.cochrane.de/cochrane/hbook.htm).

In general, a team of investigators formulates specific questions about a problem that is currently controversial, reviews the available peer-reviewed literature, identifies articles that are based on scientific methods as opposed to those reporting anecdotal experiences, and proposes a synthesis of information that summarizes the best available scientific evidence. This approach has been applied principally to the diagnosis and treatment of various conditions, and has resulted in the development of practice guidelines. Many of those are available on the Internet at the National Guideline Clearinghouse (http://www.guideline.gov). An EBM-related approach would also be useful for the analysis of etiologic issues such as the carcinogenicity of asbestos exposures. Rosoff[138] suggested that the courts are likely to use such guidelines in the future and has proposed the establishment of a voluntary federal program for directing that process. It would give the "certified" guidelines weight as evidence in health care litigation.

Controversial Issues Regarding the Causation of Malignant Mesothelioma by Asbestos Exposure

The first step in an EBM-associated approach to any problem is to formulate specific questions that need to be addressed via scientific information. These are considered below.

1. What is the minimal duration of exposure to asbestos needed to develop MM, in relation to fiber type and the circumstances of exposure?

To our knowledge, there are no scientific data that can be used to answer these questions consistently. Consequently, this issue is controversial. Plaintiffs' "experts" have quoted exposure periods as short as a few weeks as sufficient to implicate asbestos exposure as the cause of MM, without reference to the type of asbestos. Whereas defense "experts" hold that exposures of several years are necessary for such mineral groups as chrysotile.[100,139-149] This issue becomes even more problematic in cases concerning different asbestos-containing products that were used over variable periods of time. In an EBM-related context, it is usually unclear that MM would have been caused by any given exposure.

2. What evidence other than verbal assertion is needed to accept the causation of MM by alleged asbestos exposure?

Plaintiffs' "experts" universally accept verbal allegations of asbestos exposure as "evidence" of exposure above background levels (EABL), and believe

that these can be used conclusively to establish the causation of MM.[64-70,72-74] In contrast, defense consultants stress the need for objective evidence of EABL, as provided by radiologic studies, histopathologic findings, or tissue fiber-burden analyses. Ironically, even if these tests are performed, their results have been interpreted in conflicting ways. For example, if the lung tissue from a MM patient with a stated history of long-term exposure to chrysotile-containing asbestos products shows fiber burdens in the background range for the laboratory performing the test, those results could be used by the defense to conclude that the individual was not significantly exposed. However, plaintiffs' "experts" are likely to counter that argument by asserting that chrysotile is cleared from the lungs within months of exposure, and claim that fiber-burden analyses are inaccurate for that mineral group.[150-153] Conversely, above-background concentrations of chrysotile in the lung would raise different issues. The defense position would be that chrysotile does not cause MM at all, as suggested by some large epidemiologic studies; on the other hand, plaintiffs' attorneys typically disagree with that contention.[36]

3. What is the role of radiologic evidence for increased asbestos exposure as confirmation of alleged exposure to asbestos?

Defense witnesses with experience in interpreting medical imaging studies believe that there is a need for radiologic findings that suggest EABL to asbestos, such as pleural plaques or pleural calcifications (which, taken together, identify roughly 85% to 90% of persons with such exposures[99]), as objective evidence of causation in MM cases.[154-161] Plaintiffs' representatives disagree with that requirement and claim that imaging studies are not absolutely specific or sensitive. However, the latter argument seems inconsistent with the legal standard for "reasonable" medical certainty, which does not require more than a 51% level of confidence.

4. Does chrysotile exposure cause peritoneal MM?

Several studies of peritoneal MM have shown that this particular neoplasm almost invariably develops in individuals who are exposed to high concentrations of amphibole asbestos equivalent to fiber burdens associated with asbestosis.[142,162-171] However, an unsettled issue is whether diagnostic radiologic or pathologic evidence of asbestosis should be required before an asbestos-related causation for peritoneal MM is accepted in any given case. This problem may be moot in MM patients who have EABL to pure chrysotile products, because epidemiologic studies have shown no statistically significant causal correlation between that mineral type and peritoneal mesothelioma.[33]

5. Do industrial products that contain only chrysotile and no amphiboles cause pleural mesothelioma?

Several studies have shown no significant increases in the proportionate mortality rates or relative risk of MM in individuals who are exposed to a variety of pure chrysotile-containing products (eg, joint compounds, filters, and tiles, among others).[16,20,26,107,172-175] There are anecdotal reports of workers in various occupations who were said to develop MM after exposure to similar products, but that information does not fulfill the requirements of EBM-related approaches.

6. Does chrysotile have a synergistic effect with amphiboles in the causation of mesothelioma?

Defense witnesses generally believe that there is a lack of well-designed scientific studies on whether the carcinogenicity of amphiboles is enhanced by concurrent or subsequent chrysotile exposure.[176] Nonetheless, that hypothesis has indeed been cited by plaintiffs' "experts" to assign the causation of MM to chrysotile in persons with mixed exposures.

7. Is there a universally-accepted list of occupations that are at risk for the development of MM as a result of asbestos exposure?

To our knowledge, no consensus exists in medicine or the legal system on which occupations are at undeniably increased risk for the development of MM. Many clinicoradiologic and clinicopathologic reports describe individual MM patients who have developed mesothelioma after alleged occupational, paraoccupational, or household asbestos exposures of various types.[16,19,29,51,69,158,177-205] However, it could well be argued that these anecdotal reports do not provide any real scientific evidence for causation according to EBM. The "strength of association" criterion requires the study of a group of affected individuals and of a matched control group. The demonstration of statistically significant differences between both groups must be demonstrated in that paradigm. Well-designed epidemiologic studies of thousands of workers have shown significant increases in proportionate mortality rates, relative risk, and other

measures of risk in asbestos miners, workers in ship construction, insulators, pipefitters, and selected other vocational settings.[206-213] In contrast, individuals such as painters, construction workers, and auto mechanics lack significantly increased risks for the development of MM.[206-211,213-218] Once again, EBM would appear to require that objective, individually-determined indicators of EABL to asbestos should be present before that mineral group is accepted as causative in any given case of mesothelioma. This approach would obviate the legal arguments that surround occupational groups and MM.

8. Is membership in an "at-risk" occupation needed to support a role for asbestos in the causation of MM?

To our knowledge, the courts do not make such a stipulation at the present time, nor have they done so in the past. The comments made above, regarding EBM-related investigations of individual cases, again are pertinent here in providing a scientific approach to this issue rather than one that is vague and subjective.

9. What are the criteria needed to link MM causally to alleged paraoccupational or household asbestos exposures?

Knowledgeable individuals in the field of oncology accept the fact that MM can be idiopathic. In other words, it may develop in individuals who have only background exposures to asbestos, and therefore the tumor cannot be linked etiologically to that mineral group in those instances. Asbestos is ubiquitous in industrial and even some rural societies, at levels that have no known carcinogenicity in conditions of ambient exposure. Indeed, cases of idiopathic MM were described as early as 1870.[36] The presence of MM in children, where the age of the patient is much less than the required latency period of 10 to 15 years, also supports the existence of idiopathic mesothelioma.[219-222] The incidence of MM before the widespread use of asbestos in industrial societies has been calculated at 1 to 2 cases per one million people.[36] Exposure to erionite, a non-asbestiform mineral restricted to regions of Turkey, has also been shown to cause MM.[223-226] Prior therapeutic irradiation, chronic serositis, and chronic pleural or peritoneal infections are also accepted etiologies for MM.[227-232] Intense legal debates continue over the validity of "paraoccupational" or "household" exposures to asbestos and the causation of MM by those exposures. It would be logical to require a standard scientific approach to that issue in the framework of EBM, predicated on objective indicators of EABL. Otherwise, virtually any person with MM in industrial society could assert that he or she developed that tumor because of some asbestos exposure, whether it was real or imagined.

10. Is there a scientifically valid method to apportion causation of mesothelioma in instances of exposure to multiple asbestos-containing products?

There is no established scientific method that can be used to apportion relative causation to various asbestos exposures in MM cases, although "simulation of exposure" exercises have been applied to this question.[233,234] The validity of the latter techniques is questionable.

11. Is there a dose-related threshold for the causation of MM by asbestos exposure? What is the minimum concentration of asbestos in tissues that is needed to cause MM?

The presence of above-background numbers of asbestos bodies and fibers in lung tissue in individuals with MM provides reliable evidence of EABL to asbestos. However, that finding does not necessarily equate with certain carcinogenicity, because similar asbestos burdens can be seen in patients who do not have malignancies.[34-36] Despite the latter caveat, fiber burden analyses and histologic examination of tissue sections of lung represent the most direct objective means of determining EABL to asbestos in an individual case of MM. These analyses have shown undeniably that two populations of patients with mesothelioma exist: one with "background" levels of asbestos in pulmonary tissue (causally "idiopathic" cases), and another with substantially higher fiber burdens that are clearly distinct from the first group numerically.[99,101] Nevertheless, such findings do not address the question of individual "thresholds" of EABL to asbestos that are necessary for causation of MM. All that can be stated scientifically is that a threshold effect is indeed apparent in population studies of asbestos-related MMs, and that any given patient's carcinogenic "threshold" lies somewhere within the second group of fiber burden values just mentioned above.

12. Does a method exist to assess personal susceptibility for development of MM as a result of asbestos exposure?

In the thinking of the lay public, it is intuitive to assume that a patient with mesothelioma must have a particular susceptibility for development of that

unusual neoplasm. In fact, rare examples of familiar MM have been documented, and these suggest that some individuals do have a genetic predisposition to develop that tumor.[33] The "personal susceptibility" issue has been raised by attorneys to suit either the plaintiffs' or defense agendas, but in fact there are no current scientific methods that establish the existence of "individual" or "idiosyncratic" susceptibility to MM.

Conclusions

This brief consideration of a complex topic has tried to demonstrate that, although the carcinogenicity of amphibole asbestos groups is well known, there are many aspects of the association between asbestos exposure and the development of MM that are contentious in the current legal climate. Because medicolegal witnesses are still allowed to provide opinions that are based on inconclusive or deficient scientific premises, there is a need for objective guidelines regarding the causation of MM by asbestos that could be used by the court in a consistent and fair manner. Multidisciplinary studies that are well-grounded in EBM should be performed to establish these guidelines and outline pathways of research that can refine them in the future.

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