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CAUSATION IN TOXIC TORT LITIGATION: THE ROLE OF EPIDEMIOLOGIC EVIDENCE

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Summary

Epidemiology has played an important role in litigation involving alleged chemically induced illness. Epidemiologic studies can be used to examine the issue of disease causation. This article discusses basic epidemiologic concepts, including criteria for causal inferences, and their relationship to legal causation. The standard of proof in a lawsuit and the judicial decision-making process are reviewed. Limitations imposed by the nonexperimental nature of epidemiology are discussed in the context of litigation. Potential procedural barriers to the use of epidemiologic evidence are considered. The utility of such evidence is more likely to be influenced by substantive rather than procedural limitations.

Introduction

Lawsuits for illnesses alleged to be caused by toxic chemicals ("toxic torts") have become commonplace. To prevail in such litigation, a plaintiff usually must demonstrate that his or her illness was caused by exposure to a substance or mixture traceable to an identified defendant. Litigants may use epidemiologic evidence in such lawsuits to prove or dispute the issue of disease causation.

Epidemiology is concerned with patterns of distribution of disease in populations. Although the origins of the discipline can be traced back several hundred years, principles of causal inference for chronic, noninfectious disease have been explicitly articulated only recently [1–4]. Until the formulation of these principles, expert medical testimony about causation of disease by chemical and physical agents was mainly conjectural. Even now, expert testimony on issues of disease causation remains largely the domain of the physician, whose epistemologic approach to causation has usually been impressionistic, relying more on anecdotal case reports than epidemiologic studies.

This article will discuss epidemiologic concepts and criteria for inferring causal relationships, and their relationship to legal causation. Although the results of epidemiologic investigations have sometimes played a critical role in litigation, the utility of such evidence can be affected by the nonexperimental

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nature of epidemiology. Some generic limitations of epidemiologic evidence will be briefly surveyed. In addition, certain procedural limitations on the introduction of such evidence will be described.

Epidemiologic studies and relative risk

Epidemiologic studies that can be used to address the issue of causation compare the rate of disease in a population exposed to a substance or mixture with the rate in an unexposed (or less exposed) reference population. In *cohort studies*, a study population is selected on the basis of its exposure status and is followed through time to determine the subsequent disease incidence. Most causal associations between toxic exposures and chronic disease have been based on occupational cohort mortality studies. In such studies, employment records are used to identify a cohort of people exposed to one or more toxic materials. Generally, both exposure and deaths have occured prior to the initiation of a cohort mortality study; thus the follow-up consists of analyzing the causes of mortality of the cohort as compared with those of a reference population over several decades.

Another type of epidemiologic investigation useful for assessing causality is the *case-control study*. Persons with the disease of interest (cases) are compared with persons without the disease (controls) with respect to their past exposures. Ascertainment of exposures may be achieved through questionnaires or by documentary evidence (e.g., industrial hygiene surveys and personnel records), or both. Thus, case-control studies start with disease and look backwards to determine exposure, whereas cohort studies start with exposure and look forward in time towards disease incidence.

Disease rates in the exposed and unexposed populations are often compared by means of the relative risk (RR):

$$\mathrm{RR} = \frac{\text{disease rate in exposed population}}{\text{disease rate in unexposed population}}$$

For example, the average relative risk of lung cancer due to cigarette smoking is about ten [5]. This means that smokers have about a ten-fold greater likelihood of developing lung cancer than nonsmokers. A case-control study cannot directly assess relative risk. However, the usual measure of association between exposure and disease obtainable through case-control studies, the exposure odds ratio, closely approximates the relative risk for rare diseases [6].

Cohort studies permit investigation of whether there is an association between exposures and multiple disease outcomes. In contrast, a case-control investigation examines one disease in relation to one or more exposures. A case-control study, therefore, cannot provide information on the range of del-

eterious effects that may result from a given exposure. Furthermore, since most occupations are relatively uncommon, particular occupations (i.e., exposures) will be rare among cases and controls, making it difficult to detect an association [7]. Thus, occupational or environmental exposures to chemicals are often investigated using a cohort design, while case–control studies are useful to study other (more common) exposures, such as smoking, diet, and exposure to drugs.

Concepts of cause in epidemiology

Epidemiologists trace the origins of their discipline to the early 17th century [1]. Principles of causal inference for infectious diseases were proposed in the mid-1800s, and have been modified as technological advances have made the original causal postulates obsolete [8]. Similar principles for chronic, noninfectious diseases (see below) were proposed only in 1959, in large part to establish a conceptual framework by which to assess the then-controversial existence of a causal relationship between smoking and lung cancer [2–4]. As noted below, these principles are in the nature of guidelines, not formal criteria.

Several difficulties inherent in the study of chronic diseases in human populations hindered the evolution of such principles. First, epidemiology is a nonexperimental discipline in which the comparability of exposed and control groups through randomization is rarely achievable (except in clinical trials). Second, the long time lag between exposure and expression of chronic diseases such as cancer and coronary artery disease has limited the ability of investigators to conduct prospective studies. Third, many diseases, such as various forms of cancer and birth defects, may occur in the absence of a specific exposure (background incidence), indicating that, unlike most infectious diseases, more than one causal pathway may be operative.

In this complex environment, the primary basis for a causal judgement is whether people exposed to a putative cause develop the effect (disease or condition) more frequently than those who are not exposed. The search for such causes is predicated on the idea that intervention in the causal sequence can alter the outcome: if the risk of disease is increased by exposure, then decreasing the latter should diminish the risk. Such causes are often labelled "risk factors", and may, in contrast to popular concepts of cause, be neither necessary nor sufficient to bring about disease. An oft-cited example is cigarette smoking, widely regarded as the principal cause of lung cancer. Since lung cancer also develops in nonsmokers, smoking is not a necessary antecedent, and since most smokers do not develop lung cancer, smoking cannot provide a sufficient causal explanation, either. The same can be said of any of the recognized occupational causes of lung cancer, such as arsenic and chromium. Basically, the epidemiologic notion of cause is probabilistic [9]. This usage of the concept of causation, however, has been criticized as too loose and poten-

tially misleading [10]. Another view is that epidemiologists' "causes" are only components of sufficient causes [11].

Epidemiologic "causes" provide some understanding of disease etiology, yet possess limited explanatory power in the absence of basic scientific knowledge about the pathogenesis of chronic disease. For example, why most smokers do not develop lung cancer is unlikely to be explainable in the near future. This example also illustrates the obvious but significant point that individual susceptibility, other toxic exposures and unidentified risk factors may all play important roles in determining whether chronic disease will develop. Such factors are of less importance when acute exposure to the chemical in question is highly toxic, such as occurred at Bhopal. In such a case, a common biological response to the exposure may overwhelm the factors underlying individual susceptibility.

Principles of causal inference from epidemiologic data

Numerous authors have articulated principles of causal inference from epidemiologic studies [1,2,4,9,12]. In applying such principles, one usually assumes that a statistically significant association between a risk factor and disease has been demonstrated. To evaluate whether the observed association represents a true etiologic relationship, the following criteria are generally considered: (1) appropriate temporal sequence of events, (2) methodological validity of the investigation(s), (3) strength of the association, (4) consistency of results among different studies, (5) biological gradient of effect, (6) biological plausibility and supporting experimental evidence, and (7) specificity of effect*. Of these, the temporal sequence is clearly a *sine qua non* and the validity issue is very nearly of the same status. These criteria are generally considered tools for analysis of a body of literature: rarely will a single positive study suffice as the basis for a causal inference.

Temporal sequence

It is obviously important to ascertain that the putative cause (or exposure) occurs before the effect. In practice, however, it may sometimes be difficult to determine the sequence, especially in case–control studies. For example, aluminum silicates have been identified in sites of neural pathology in people with

*Other criteria listed by Hill [4] include coherence and analogy. Coherence means that "the cause-and-effect interpretation of [the] data should not seriously conflict with the generally known facts of the natural history and biology of the disease [4]". For practical purposes this criterion is not distinguishable from biological plausibility. Analogy is so nonspecific that as a criterion for deciding whether an association is causal it offers little guidance. The broad generality of Hill's examples, e.g., if one drug or virus causes birth defects so could another, may be useful in suggesting hypotheses, but cannot be considered nearly so important in determining causality as the seven criteria described in the text.

Alzheimer's disease, but it is unknown whether this phenomenon is a cause or consequence of the disease process [13].

Methodological validity of the investigation(s)

Validity is somewhat different from the other criteria in that it primarily affects the relative weight one accords particular studies in assessing causation, rather than the inference of causation itself. Although this criterion encompasses many concerns, the most important is whether confounding and other biases have been appropriately managed in the design and analysis of the study. Failure to control for confounding variables or to identify potential biases in the design of the study can invalidate any conclusions regarding causality. Confounding occurs when an extraneous (causal or risk) factor is associated with both the disease and the exposure. An increased risk that appears to be due to the exposure of interest may in fact be due to the extraneous factor, which is disproportionately represented among the exposed population. Cigarette smoking is a common confounder in studies of industrial exposures and lung cancer. Smoking is an independent cause of lung cancer and is more common among people in blue-collar occupations than in the general population (the usual reference population in occupational studies). Thus, the increased incidence of lung cancer seen in some industrial cohorts may be due (at least in part) to smoking.

Strength of the association

The stronger the association, i.e., the greater the magnitude of the relative risk or odds ratio, the greater the probability of the existence of a causal relationship. Confounding and bias may explain some weak associations, but are not likely explanations of large relative risks. If the association were due to a confounding variable, the relative risk from exposure to the confounder would have to be at least as large and theoretically easily detectable.

Consistency of results

In epidemiologic studies biases may arise in the collection and analysis of historical data. Therefore, belief in a causal relationship is strengthened if an association is consistently observed in a variety of investigations involving different study populations and designs. Even if a given study were affected by bias or a spurious association, it is less likely that these shortcomings would apply to other study conditions. On the other hand, the inference of causation is weakened if similar types of studies yield qualitatively different results.

Biological gradient

The criterion of a biological gradient is met when there is a progressive increase in the incidence or severity of disease with increasing duration or intensity of exposure — i.e., when there is an observable dose–response curve.

In occupational cohort mortality studies, past exposures can sometimes be classified as low-, medium-, or high-level, permitting investigation of a dose–response relationship. If exposure is described as only exposed versus unexposed, however, no such determination of a biological gradient is possible.

Biological plausibility and experimental evidence

It is helpful if a causal inference is consistent with current knowledge about the relevant biology and pathophysiology of the disease. Limitations of current thinking may, however, make this criterion somewhat soft. For example, initial reports of an association between cigarette smoking and bladder cancer were considered unlikely by some because a plausible mechanism (now thought to involve pulmonary absorption of mutagens and other carcinogens subsequently eliminated through the urine) had not yet been postulated. If an epidemiologic study suggests that exposure to a substance causes cancer in humans, ancillary evidence of carcinogenicity in animals and of genotoxicity *in vitro* or *in vivo* is useful (but not strictly necessary).

Specificity of effect

Specificity suggests that a cause should have a single effect, a proposition carried over from earlier principles of causation for infectious disease [2]. For example, lack of specificity was cited as evidence that cigarette smoking does not cause lung cancer [12]. If present, specificity supports a judgement of causality, but its absence is not critical, simply because many toxic substances produce a variety of adverse effects. Even in those instances where specificity of effect has been adduced — e.g., asbestos and mesothelioma, vinyl chloride and liver angiosarcoma — these substances have also been shown to be responsible for other effects as well (i.e., elevated risks for lung cancer). Furthermore, environmental and occupational exposures often involve multiple chemical substances, which may produce diverse effects. Where multifactorial causation is common, specificity is not usually a valuable concept.

As noted above, these are not rigid criteria, nor are there rules for applying them or rating their importance relative to one another. Judgement of causality in epidemiology is essentially an informal, subjective process [12].

Standards of proof in litigation

In personal injury cases the plaintiff must prove each element of his case by a "preponderance of the evidence". For example, a plaintiff must demonstrate that it is more likely than not that the defendant was the source of a chemical or mixture to which the plaintiff was exposed, that the plaintiff suffered an injury or illness, and that the exposure caused the injury or illness. Although theoretically a preponderance of the evidence can be expressed as a probability

greater than 50 percent, typically the standard is not expressed quantitatively. Indeed, to do so would lead to the uncomfortable conclusion that a plaintiff demonstrating the elements of his case with a 49.99 percent probability would lose, while another making a showing with 50.01 percent probability should prevail. Commentators have observed that while mathematical expressions of probability of the standard of proof are applicable in principle, they are not practically calculable "because of the complexity of human affairs, the paucity of relevant statistical data, or the difficulty of measuring intensity of belief" [14]. Others have suggested that quantitative expression of probabilities may mislead the judge or jury [15]. Regardless of the underlying intellectual rationale, the standard of proof invoked in the courts is intuitive and qualitative, not quantitative.

In applying this standard of proof, courts have distinguished causation which is medically "possible" from that which is medically "probable". For instance, in *Parker* v. *Employers Mutual Liability Insurance Co.*, 440 S.W. 2d 43 (1969), the plaintiff unsuccessfully argued that his occupational exposure to radiation caused his cancer. Some physicians testified that it was possible that radiation exposure could cause cancer, while others stated that no causal relationship could be inferred. The court held that "[A] possible only becomes 'probable' when in the absence of other reasonable causal explanations it becomes more likely than not that the injury was a result of its action" (at p. 47). Other courts have expressed this requirement under the rubric of a "reasonable medical certainty", an ambiguous term that has been a source of some confusion in the courts [16,17].

Strict application of the preponderance of the evidence standard would mean that, except in instances where a specific, direct relationship between the exposure and the disease has been previously established, plaintiffs with chronic illnesses alleged to be due to exposure to toxic substances will not be able to prove their cases. The causes of most chronic diseases are unknown and will remain so in the near future. Although absolute scientific certainty has never been a prerequisite for winning a lawsuit, lack of knowledge about causation (particularly for illnesses and conditions such as cancer or birth defects) is probably the weakest part of the plaintiff's case. For example, a plaintiff with colon cancer might claim that his disease was due to exposure to nitrosamines and organic solvents found in his water supply. Ignoring, for the sake of argument, that the etiology of this disease is obscure, the plaintiff would still have to overcome the defendants' contention that: (1) the plaintiff's normal diet contains much higher concentrations of carcinogens than the contaminated drinking water; and (2) therefore, another reasonable causal explanation exists for the plaintiff's disease [18]. Difficulty in refuting such arguments has generated calls for selective reform of the tort law system that would, among other things, modify plaintiffs' burden of proof of causation [19].

There are, however, instances in which the preponderance of the evidence

standard would not be difficult to meet. Any plaintiff demonstrating a significant, appropriately timed exposure to a substance or mixture meeting most of the epidemiologic criteria for causal inference should be able to sustain the burden of proof. This occurs most often where the plaintiff has experienced high-level occupational exposures, though even in the context of environmental contamination there are occasional examples of this. For instance, Baker et al. [20] described an investigation by the federal Centers for Disease Control of possible lead poisoning in people living near a primary lead smelter. Human body burdens of lead varied inversely with the distance of residence from the smelter, as did lead levels in air, dust and vegetation. Anemia and neurological deficits characteristic of lead toxicity were found in children with elevated lead levels — i.e., those living nearest the smelter. When emissions from the smelter decreased, so did the children's blood lead levels. In this example, all the elements of a plaintiff's case could be established by a preponderance of the evidence.

Principles of causation in tort law

In tort law the term causation embraces the concepts of factual causation ("causation-in-fact") and "proximate cause". Factual causation, i.e., whether the defendant's conduct or product caused injury or illness to the plaintiff, is generally determined by a jury. If, however, the undisputed facts are such that reasonable people could not differ in their interpretation, the judge may dictate how the causation issue should be decided. "Proximate cause" is a policy issue: assuming that causation-in-fact is demonstrable, should the defendant be held legally responsible for the harm which befell the plaintiff? This depends on whether the defendant's conduct was close enough in the chain of causation to the actual harm to the plaintiff that the adverse effects of this conduct were "reasonably foreseeable". This is often phrased in terms of whether the defendant had a duty to protect the plaintiff against the type of event that occurred [21]. Theoretically proximate cause might be an issue where past chemical exposures have resulted in the delayed expression of disease; however, determination of causation-in-fact is operationally of greater importance in toxic torts.

The principal criteria used by juries in determining causation-in-fact are the "but for" test and the "substantial factor" formula. Under the "but for" test, an act or omission of the defendant is said to be a cause of an event if the latter would not have occurred "but for" the defendant's conduct. In cases involving injury or illness due to acute exposure to toxic substances with well characterized toxicity, such as methyl isocyanate, the "but for" criterion will be relatively easy to satisfy. For other disease outcomes that may occur even in the absence of exposure to particular chemicals, e.g., lung cancer in an industrial worker who is a smoker, it is unlikely that a plaintiff could establish factual

causation in a court employing the "but for" rule. In such instances there is clearly a tension between this strict legalistic approach to causation and the epidemiologist's probabilistic notions of cause or risk factors.

This antinomy is avoided, however, in courts that rely on the "substantial factor" formula. Under this approach, "the defendant's conduct is a cause of the event if it was a material element and a substantial factor in bringing it about" [21]. This standard is clearly an improvement over the "but for" rule from the plaintiff's perspective. Elaborating the example in the previous paragraph, consider a case of lung cancer arising in a worker, intermittently exposed to asbestos, who has smoked a pack of cigarettes a day for 20 years. In this instance cigarette smoking and asbestos exposure both carry elevated relative risks of lung cancer, i.e., ten and five, respectively [22]. When both are present, there is an apparent interaction between the exposures, resulting in a relative risk of about 50 [22]. Depending on the facts, a jury might reasonably conclude that the asbestos exposure was a substantial factor in the evolution of the plaintiff's lung cancer, but this is not a foregone conclusion. For example, the defendant (an asbestos manufacturer or plaintiff's employer*) may be able to demonstrate that the plaintiff's asbestos exposure was substantially less than that of the cohorts investigated epidemiologically, so that the risk imparted by asbestos exposure would be lower than those noted above. Each case is evaluated individually.

Both the "but for" and the "substantial factor" formulations are viewed as the lowest common denominators of the jury's decision-making [22]. In other words, jurors are asked to apply one or the other in an intuitive, commonsense manner to decisions about causation. In most instances involving mechanical or immediate causation, such an approach will operate well, since the effects of physical actions and the short time interval between the cause and effect can be easily appreciated. Most people would not have trouble inferring that the release of a large quantity of a dessicant gas caused acute respiratory symptoms a few minutes later in a residential neighborhood downwind of the release.

However, this intuitive approach to the determination of causation has led to wrong decisions in cases of chronic diseases such as cancer. In cases involving a long latency between the occurrence of the alleged cause (e.g., exposure to a carcinogen) and the effect, courts have generally been reluctant to grant relief [23]. For example, in the leading case of *Miller* v. *National Cabinet Co.*, 8 N.Y. 2d 277, 168 N.E. 2d 811 (1960), the court held that 25 years of working with benzene could not have caused the plaintiff's leukemia because the latter occurred several years after he had retired. Courts have been uneasy with the concept of latency because another cause could intervene in the interim. Latency is also a less facile concept for juries than simple mechanical causation

*The context of workers' compensation litigation presents an even more flexible criterion for causation: "arising out of and in the course of employment".

[16]. Thus, for decades, plaintiffs in numerous jurisdictions prevailed in actions alleging that their cancers were due to trauma preceding the discovery of the cancer by as little as two weeks [24]. Considering, however, that epidemiologists and physicians had themselves not developed coherent concepts of causation for noninfectious diseases until relatively recently, it is not surprising that there have been inconsistent and scientifically implausible judicial decisions.

Causation in the courtroom is clearly not the same as that considered by epidemiologists. There are some superficial similarities: the "substantial factor" formula is conceptually consistent with epidemiologic "risk factors". Judgements about causation are subjective and informal in litigation and in epidemiology. Fundamental differences, however, cannot be overlooked. Epidemiology is concerned with statistical associations involving populations and therefore conclusions about causation refer not to individual cases, but to categories of events. Litigation, on the other hand, is a process of resolving disputes among individuals. Litigants must prove causation in individual cases by a preponderance of the evidence. Epidemiologic evidence, therefore, may generally offer indirect support on the issue of causation.

Moreover, the role of the scientist differs significantly. Although evidence of disease causation must be introduced through expert testimony (see "Procedural issues", below), issues of factual causation in litigation are decided by members of the jury, referring to their experience, intuition and common sense. Relating the results of epidemiologic investigations to the matter of disease causation in individuals is the responsibility of the expert witness. The jury may heed the expert's opinion or disregard it in making its decision. In the adversarial context of litigation, experts for plaintiffs and defendants typically offer conflicting opinions on causation: inevitably the jury must choose which expert(s) to believe. Other values besides scientific validity enter the jury's decision-making process: even in the absence of epidemiologic evidence of causation a jury may still render a verdict for the plaintiff [25].

It should be emphasized that epidemiologic criteria for causal inferences may be applied by the expert witness, not the judge or jury. The judicial standard is whether the plaintiff has demonstrated his case by a preponderance of the evidence. There is no epidemiologic evidentiary standard in litigation: some have argued that its absence has fostered inappropriate decisions by the courts [24].

Finally, conclusions about causation in epidemiology evolve with new knowledge. In contrast, resolution of a lawsuit represents a final determination of the issues between the litigants. For instance, since 1960 substantial epidemiologic support for a benzene–leukemia relationship has accumulated, but the plaintiff (or the plaintiff's estate) in *Miller* v. *National Cabinet Co.* (discussed above) could not relitigate the case based on subsequent scientific developments.

Uses of epidemiologic studies in litigation

As noted above, epidemiology involves investigations of populations, not individuals, and can provide circumstantial evidence regarding causation in an individual case. In some cases, however, epidemiologic evidence can bear directly on the issue of causation for all individuals in a given class. This is particularly true where the exposure is strongly associated with a rare disease, e.g., asbestos and mesothelioma, prenatal exposure to diethylstilbestrol and clear cell vaginal adenocarcinoma, occupational exposure to vinyl chloride and hepatic angiosarcoma [24]. The contexts in which epidemiologic evidence may be used include: (1) supporting causation where plaintiffs are not members of the study population; (2) supporting causation where plaintiffs are members of the study population; (3) providing evidence that plaintiffs, while not currently ill or injured, have been subject to exposure that puts them at risk for future harm; (4) disputing the existence of a postulated causal relationship. These topics are discussed in the following paragraphs.

Plaintiff not in study population

As circumstantial evidence of proof, epidemiologic studies may be used to support expert testimony regarding whether an exposure is capable of causing the harm alleged by a plaintiff. This situation typically arises in workers' compensation cases and tort litigation premised on theories of negligence or products liability. Where the epidemiologic evidence is strong (e.g., asbestos cases), plaintiffs have usually, but not always, prevailed [26]. Where epidemiologic evidence for causation is not as compelling (e.g., leukemia due to exposure to ethylene oxide), the outcome will be less predictable.

Plaintiff is in study population

Where the plaintiff is a member of the study population, the evidentiary issues become somewhat thornier. If the disease can also occur in the absence of exposure, then the evidence proferred might be characterized as "naked statistical evidence", which courts have traditionally been reluctant to admit (see below) [27]. In order to meet the "preponderance of the evidence" standard of proof, the epidemiologic investigation should in theory demonstrate a relative risk of at least two [24]. Only in these instances could an individual plaintiff credibly claim that his illness was more likely than not due to the exposure. Demonstration of such increased risk represents a minimum requirement: other epidemiologic criteria for causation must also be fulfilled.

A recent example illustrates the relationship of increased risk and the preponderance of the evidence standard. Two epidemiologic studies examined pregnancy outcomes in women whose drinking water supply had been contaminated by several organic solvents that had leaked from an underground storage tank [28]. A lawsuit arising from this incident (involving hundreds of

plaintiffs and several defendants, including the microelectronics firm that operated the storage tank) was recently settled before trial. Congenital cardiac defects showed a relative risk of 2.6 in the affected census tract compared with the rest of the county, while odds ratios for spontaneous abortions and total congenital anomalies were 2.4 and 3.1, respectively. Despite these significantly elevated risks, other issues raised in the epidemiologic investigations implied different legal outcomes for the cardiac defects versus the other anomalies and the spontaneous abortions. Exposure to water contaminated by the solvent plume was shown to be inconsistent with the geographical and temporal distribution of cardiac defect cases. Such cogent disproof did not obtain in the cases of spontaneous abortions and total congenital anomalies, nor could the excess cases be explained by differences in other known risk factors. In this litigation, therefore, the epidemiologic evidence would have weakened the plaintiffs' arguments insofar as the cardiac defects were concerned and would have had the opposite effect on the other cases.

Proof of future harm

Medical opinion evidence regarding future consequences of present injuries is typically admissible when phrased in terms of probabilities or "reasonable medical certainty" [29]. The issue of future consequences of a known exposure to a substance with delayed toxic effects arises less frequently, and then usually in the context of a regulatory dispute. However, epidemiologic evidence of causation may used as the basis for an injunction to prevent exposure or to prove increased susceptibility to future disease, decreased life expectancy, or fear of future illness arising from exposure [30]. In *Reserve Mining Company* v. *Environmental Protection Agency*, 514 F. 2d 492 (8th Circ. 1975), the court found that the defendant's discharge of asbestiform fibers into the air near Duluth, Minnesota and the water of Lake Superior constituted a potential "risk to public health of sufficient gravity to be legally cognizable", justifying orders to abate such emissions. Epidemiologic studies indicating both occupational and nonoccupational risks of cancer from airborne exposure were the principal basis for the court's order to abate air emissions immediately, while permitting a more leisurely abatement of emissions in the drinking water supplies of 200,000 people. That the court was even willing, however, to issue an injunction ordering abatement of the water pollution is interesting because of the lack of compelling human or animal evidence that ingested (as opposed to inhaled or implanted) asbestos is carcinogenic. In this case there appeared to be legal cause-in-fact in the absence of demonstrable scientific cause-in-fact [31].

Disputing causation

Negative epidemiologic studies may also be used to discount or disprove risks from exposure; however, such use tends to be narrowly circumscribed because

of the limited sensitivity of the methodology. A spurious positive result may be due to bias or confounding. In contrast, a spurious negative study may be due to bias, confounding, inadequate sample size (few epidemiologic studies can detect less than a doubling of relative risk), excessive loss to follow-up (in cohort studies), not allowing for a sufficient latency for diseases such as cancer, inappropriate choice of a reference population, and lack of exposure (of the entire "exposed" population or a substantial proportion thereof). A paper by Morgan et al. [32] on the mortality experience of ethylene oxide production workers is illustrative. One of the stated concerns for undertaking this study was the possibility of ethylene oxide-induced leukemia. Yet the size of this cohort (767 men) militated against an adequate investigation of this issue: a more than ten-fold increase in leukemia deaths (over expected rates) would have been the minimum statistically significant excess detectable. Furthermore, an industrial hygiene survey of the facility disclosed that, because of many engineering precautions (including out-of-doors reaction systems), there was virtually no ethylene oxide detectable in work areas. Not only was the study population too small to detect anything other than an enormous effect, but even if there had been a larger study population it would appear that exposures had been exceedingly low. Thus, this study could have been predicted *a priori* to have a negative outcome, which clearly does not imply a lack of effect.

Limitations of utility of epidemiologic studies

Causal associations established by epidemiologic investigations have been determinative of the outcome of many lawsuits involving relatively few substances — e.g., asbestos, benzene, vinyl chloride, and diethylstilbestrol. It is likely that successful litigation premised on such studies will continue to include a small number of toxic materials for which prior exposures can be reasonably well characterized. Several methodological limitations, discussed briefly below, preclude an adequate epidemiologic assessment of the risks of chronic effects of exposure to most chemicals.

The vast majority of epidemiologic studies documenting a delayed effect of specific chemicals on, e.g., risks of cancer or adverse reproductive outcomes, involve relatively high-level human exposures. Typically the context is occupational (e.g., bis-chloromethyl ether), medical (thalidomide, diethylstilbestrol) or personal habits (cigarettes, alcohol). Not only is one more likely to detect an effect with high doses, but also such exposures can be documented. Exposures to putative carcinogens, teratogens, or other toxic substances experienced by the general population in air, food, and water are usually at much lower levels and would be expected to impart a lower risk that, in most circumstances, would not be detectable epidemiologically. For example, extrapolating from the carcinogenic potency of DDT in animals, it has been suggested that a case–control study large enough to detect a statistically significant effect

would have to include about two billion study subjects [33]. A legal corollary of this issue of statistical power is that if the risks are too small to be readily detectable by epidemiologic methods, then no plaintiff should be able to meet the preponderance of the evidence standard.

In occupational settings delayed effects of most chemical exposures cannot be effectively studied epidemiologically [34]. Small study populations, multiple exposures (i.e., potential confounding), and inadequate documentation of past exposures all make adequate epidemiologic investigation difficult. On the other hand, specific industries, as opposed to individual chemicals *per se*, are amenable to such analysis using a cohort design. Well designed occupational cohort studies can ascertain whether particular industries (or jobs) are associated with excess risks of chronic diseases; however, specific causative exposures may not be identifiable.

Another major issue concerning the validity of such studies is bias. For example, case–control studies relying on questionnaires to ascertain exposure are subject to recall bias, in which the experience of an adverse outcome among the cases may influence the recollection of exposure. Similarly, epidemiologists' or physicians' knowledge of exposure status may result in ascertainment bias [35]. Bias in selection of the study population(s) may generate spurious results that cannot be corrected in the analysis. One form of selection bias that affects all occupational cohort studies in which the general population is the reference population is the "healthy worker effect". People who are working are generally healthier than those who are not or cannot, which is reflected in lower overall and cause-specific mortality.

In a situation involving persons living near a hazardous waste site, epidemiology will rarely provide conclusive information. Exposures are usually poorly characterized, the study population is typically small (which affects both the range of outcomes and the magnitude of the effects that can be investigated), and the suspicion of chemically induced illness (sometimes accompanied by participation in ongoing litigation) may bias results based on questionnaires [36]. For chronic illnesses with a long latency, such as cancer, an insufficient time may have elapsed since the first exposures. Furthermore, the uniqueness of the population's exposure makes reproducibility in other studies unlikely.

Thus, although epidemiologic evidence has played an important role in some toxic tort litigation, its influence will probably continue to be limited to lawsuits involving a relatively small number of substances.

Procedural issues

Two procedural issues affecting the use of epidemiologic evidence in litigation relate to its scientific and statistical aspects. The first concerns who should be qualified to serve as an expert witness. Second, some commentators have indicated that epidemiologic evidence could be excluded either because it is

essentially statistical or because it falls within the proscription against hearsay evidence [30].

When scientific, medical or other specialized information considered to be outside the province of common knowledge is to be introduced in evidence, there are two procedural avenues generally followed by the judiciary. First, a court may take judicial notice of a generally accepted scientific principle, which the judge and jury may assume to be true for purposes of the litigation. This procedure avoids the expense and time involved in obtaining expert testimony to establish, e.g., the reliability of Doppler-based radar equipment used by police. The second route, followed almost invariably where health-related issues of fact are in dispute, is to use the testimony of experts, who may testify not only on general scientific principles, but also on the application of those principles to the specific facts in the case [37].

In cases involving causation of disease, the courts have generally looked to the physician as the most appropriate expert witness. This has often meant anyone with a medical degree, regardless of the witness' specialized training [38]. In some areas of clinical medicine, failure to demand relevant specialization presents little problem. When the issue involved, however, is whether alleged exposures to a chemical substance caused the plaintiff's cancer or other delayed effects, "the doctor's cause is little more than the doctor's conjecture" [39]. A vast portion of medical knowledge derives from anecdotal case reports or series of cases, which are descriptive and impressionistic, and which require practically no statistical sophistication. To the extent that most practicing physicians have had little, if any, training in chronic disease epidemiology and even less in statistics, they would not meet formal criteria for an expert — i.e. "someone qualified ... by knowledge, skill, experience, training or education" [40]. Others have proposed that, at a minimum, expert witnesses testifying on chemical causation of disease be knowledgeable about epidemiology [23].

Nonetheless, some courts have been reluctant to allow nonphysicians to encroach on the domain traditionally reserved for medical doctors. Hoffman [30] cites the case of *Reyes* v. *Wyeth Laboratories*, 498 F. 2d 1264 (1974), a product liability lawsuit in which a child had developed paralytic polio shortly after immunization with an attenuated live viral vaccine. The jury chose to believe the child's attending physician, who testified that the disease was caused by the vaccine. The trial judge did not permit the Chief of the Centers for Disease Control polio laboratories to testify that the virus was caused by a wild strain rather than the vaccine strain because this expert was not a physician. More recently, with increasing recognition that experts other than physicians can provide credible testimony on issues of disease causation, courts have shown greater willingness to admit such testimony. Yet there is still a rearguard resistance to this trend. For example, Dickson [41] criticized a California court for allowing a nonphysician epidemiologist to testify that prenatal exposure to

diethylstilbestrol causes clear-cell vaginal adenocarcinoma, a proposition that is nearly beyond dispute in the medical profession.

Another procedural issue of theoretical concern in the use of epidemiologic evidence is that it may be considered hearsay and therefore inadmissible [30]. "Hearsay" is an oral, written (or even nonverbal) assertion made out of court, offered as evidence of the matter asserted [42]. An example of hearsay is a statement by a witness that someone else had said that exposure to benzene causes myelogenous leukemia. If offered in evidence to prove the truth of this causal proposition, this testimony would be excluded as hearsay. Such evidence traditionally has been considered unreliable because the person originally making the statement was not (necessarily) under oath, was not present in court (so that the judge or jury could not assess his credibility), and, most importantly, was not subject to cross-examination [38].

Technically any written assertion made out of court can be considered hearsay if the writer is unavailable as a witness. Thus, epidemiologic studies could potentially fall within the proscription against hearsay. If, however, such studies form the basis for an expert's opinion about causation, most courts would allow them into evidence, regardless of the hearsay rule [43]. If the author of the study or studies in question is the expert witness, he can reiterate his conclusion(s) in open court, in which case the hearsay rule is obviously inapplicable. There are numerous common law and codified exceptions to the rule, all of which contain "circumstantial guarantees of trustworthiness" [38]. Published studies or reviews could be admitted under the "learned treatise" exception, where the circumstances of publication (e.g., one's scientific reputation, peer review) are thought to encourage factual reliability. Studies conducted by or under the direction of government officials under authority of law fall within another explicit exception in many jurisdictions [44]. There is even a "residual" exception to the hearsay rule for situations not clearly falling within one of the recognized exceptions [44]. Thus, it should be apparent that, one way or another, information that benzene causes leukemia will be admitted. For practical purposes, therefore, the hearsay rule should not affect the introduction of epidemiologic evidence.

Courts have in the past been reluctant to accept evidence that is essentially statistical, where grouped data are offered to prove the existence of a relationship affecting the plaintiff(s). Epidemiology can be characterized as applied biostatistics; however, the principles of causal inference insure that epidemiologic evidence is clearly more than "naked statistical evidence" [27]. Furthermore, even if a particular study were adduced as something approaching naked statistical evidence (e.g., an investigation showing that people living near a hazardous waste site had a higher-than-expected incidence of adverse reproductive outcomes), there is ample judicial precedent for admitting such evidence, assuming that it can be shown that the data were collected, compiled

and analyzed reliably and according to a generally accepted methodology [25,40,45].

Conclusions

This article has discussed several basic concepts in epidemiology, including: (1) the types of studies that can be used to address issues of disease causation and one measure of risk, (2) epidemiologic concepts of "cause", and (3) principles of causal inference for chronic, noninfectious disease. The probabilistic notion of "cause" in epidemiology was contrasted with the legal approaches to "causation-in-fact". Of particular importance is that epidemiology deals with population-based data, whereas in the courtroom the causation issues are resolved with reference to individual litigants. Although epidemiologic evidence may strengthen the scientific validity of a causal inference, a jury's decision regarding causation is not limited by epidemiology. Rather, the causation question, like other aspects of the case, is judged on the basis of the preponderance of the evidence, which may include medical and other testimony not based on epidemiologic investigations.

In cases involving plaintiffs' exposure to relatively few chemicals, epidemiologic data have played a crucial role in determining the outcome of litigation. The limitations of this nonexperimental discipline, however, make it unlikely that epidemiologic evidence will play a major role in litigation involving illnesses allegedly due to specific substances, except where relatively high-level, well characterized (e.g., occupational or medical) exposures have occurred. Thus, substantive issues related to epidemiologic methodology are more likely to limit the utility of such evidence than are minor procedural issues such as judicial rules against introducing hearsay or statistical evidence.

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