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Evidence: A Brief Guide to Differential Etiology

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A Brief Guide to Differential Etiology

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Introduction

This chapter sets forth a framework by which case-specific statements about a toxic-tort claim might be inferred based on general scientific findings from toxicology and epidemiology.

Research scientists, though principally motivated by the desire to explain phenomena that have already occurred, primarily study causal effects indirectly, by elucidating and modulating the mechanisms that *generally* produce an effect rather than by directly attempting to identify what caused the effect in a *specific* instance. In court, general causation is relevant proof, but plaintiffs must ultimately prove specific causation in their particular cases. For example, while toxicologists and epidemiologists research whether benzene causes cancer generally, a court must determine whether benzene caused *this plaintiff's* cancer. This disconnect between science's focus on general causation and the legal system's demand for individual causation reflects the "group to individual" (G2i) problem endemic at the crossroads of law and science.[2]

To bridge that gap, the plaintiff normally will retain an expert to testify, using "differential etiology," that the plaintiff's injury was more likely caused by the general phenomenon than by other potential causes. Differential etiology is not defined in the scientific literature; it is a legal term, born of necessity and adopted by lawyers and courts to meet a need of the law that is not

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[1] Excerpted and adapted from Joseph Sanders, David L. Faigman, Peter B. Imrey, & Philip Dawid, *Differential Etiology: Inferring Specific Causation in the Law from Group Data in Science*, 63 ARIZ. L. REV. 851 (2021).

[2] David L. Faigman, Christopher Slobogin & John Monahan, *Gatekeeping Science: Using the Structure of Scientific Research to Distinguish Between Admissibility and Weight in Expert Testimony*, 110 NW. U. L. REV. 859, 888 (2016); David L. Faigman, John Monahan & Christopher Slobogin, *Group to Individual (G2i) Inference in Scientific Expert Testimony*, 81 U. CHI. L. REV. 417 (2014).

fully addressed by classical science.[3] Yet courts have not developed systemic guidance about the admissibility of testimony based on differential etiology. Too often, courts have viewed differential etiology as a simple matter of logical deduction rather than what it actually is: an inferential process combining statistical reasoning with a conceptual model of the causal interrelationships underlying observed data.

Relying on both law and science, this chapter seeks to bring clarity to the differential-etiology determination by providing scientifically informed guidelines for conducting differential etiology. Ultimately, the differential-etiology determination will be an individualized inquiry for each case, but the guidelines proposed here can and should inform the court's assessment.

Differential Etiology

Differential etiology in toxic-tort cases entails three evidentiary steps.

The first step is diagnosis: an expert must accurately diagnose the illness from which the plaintiff suffers. The diagnosis is itself a form of G2i inference and is part of medical training under the label of "differential diagnosis." Courts sometimes conflate the purposes of differential diagnosis and differential etiology,[4] but they serve very different functions. The former seeks to identify the ailment of concern, while the latter seeks to identify the cause of that ailment. Further, diagnosis is a core part of medical expertise; etiology is not.[5] For the practice of medicine, it is usually enough that the physician concludes that the patient in fact has cancer; the physician need not determine that the cancer was caused by benzene. The first step, then, focuses on the discrete and descriptive question of *whether* the plaintiff is injured.

The second step is general causation: an expert must

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[3] *See generally* Best v. Lowe's Home Ctrs., Inc., 563 F.3d 171, 180 (6th Cir. 2009).

[4] *See, e.g.*, Lennon v. Norfolk & W. Ry. Co., 123 F. Supp. 2d 1143 (N.D. Ind. 2000) ("Differential diagnosis is a patient-specific process of elimination that medical practitioners use to identify the 'most likely' cause of a set of signs and symptoms from a list of possible causes.").

[5] Erica Beecher-Monas, *Lost in Translation: Statistical Inference in Court*, 46 ARIZ. ST. L.J. 1057, 1058 (2014).

determine that the proffered cause of the plaintiff's injury is in fact capable of causing that kind of injury. General causation is the gravamen of scientific research. Scientific conclusions of general causation, however, are a matter of the degree of confidence, and that level of confidence depends upon the internal and external validity of the research. Internal validity considers whether the methods and statistics in the research identified a true relationship among the variables studied in the populations and under the circumstances in which the studies occurred. External validity considers the reliability of imputing that same relationship to other populations, other circumstances, and even related comparators and outcomes.[6]

The third step of differential etiology is specific causation: an expert must determine that the general cause was in fact the cause of this particular plaintiff's injury. If general causation determines that a substance *can* cause the plaintiff's condition, specific causation assesses whether the substance *did* cause the plaintiff's condition. In this third step, the expert must rule out alternative causes—known and unknown—based on extant scientific knowledge applied to the specifics of the case.

The following sections presume the availability and accuracy of a diagnosis and focus on the second and third steps: general causation and specific causation.

A. General Causation

Individual research studies tend to focus on either internal or external validity at the expense of the other. A toxicology study of a chemical's effect on mice, for example, can be tightly controlled to produce internally reliable conclusions about causation, but that study may have weak external validity—precisely because of those tight controls—for predicting the same causal relationship among humans or involving different dosages. By contrast, an epidemiological study of chemical exposure on a population of humans can produce more reliable external validity for inferring causation on other human populations and under different circumstances, but the study may have weak internal validity

[6] DAVID G. KLEINBAUM, LAWRENCE L. KUPPER & HAL MORGENSTERN, EPIDEMIC RESEARCH: PRINCIPLES AND QUANTITATIVE METHODS 181–280 (1982).

because it generally cannot rule out the possibility that the true relationship between the chemical and its effect has been distorted by the failure to account for some unmeasured variable. All things considered, we need multiple studies, using multiple methods, with high combined validity, before we can be confident that an identified relationship is true for purposes of general causation.

These features of scientific research raise the difficult question of how multiple research studies, using a wide variety of subjects and methods, and having varying strengths and weaknesses, might be considered collectively to support a hypothesized causal relationship. In a landmark article, Sir Austin Bradford Hill advanced a set of indicia to assess the level of confidence in concluding the existence of general causation:

> (1) Strength: how large the increase of risk of a disease is in those exposed to the suspected cause;
> (2) Consistency: whether the association has been observed in multiple studies in different populations and circumstances;
> (3) Specificity: whether the observed relationship is relatively specific to the substance and disease in question, rather than observed generally with many other candidate substances or diseases;
> (4) Temporality: whether the disease follows an appropriate interval after exposure;
> (5) Biological Gradient: whether the incidence or severity of the disease increases as exposure rises;
> (6) Plausibility: whether the hypothesis that the substance causes this disease is consistent with existing biological knowledge;
> (7) Coherence: whether other facts about the history and distribution of the disease support or conflict with the causal hypothesis;
> (8) Experiment: whether the incidence of the disease falls when preventive action is taken to reduce exposure; and
> (9) Analogy: whether similar exposures are known to cause similar diseases.[7]

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[7] Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 PROC. ROYAL SOC'Y MED. 295 (1965).

The set of Bradford Hill factors can be a useful tool for courts assessing the existence of general causation.[8]

B. Specific Causation

Both as a matter of common sense and scientific research, some circumstances supply an overwhelming basis for connecting a particular cause to a specific condition. Temporal proximity, for example, can be indicative of specific causation, such as when an acute exposure to a toxin is followed immediately by an illness shown to be generally caused by such exposure, with no other plausible causes.[9] So-called signature diseases are another, albeit a rarer, example of how the specificity of circumstances can lead to specific causation: asbestosis is always caused by, and mesothelioma is nearly always caused by, asbestos exposure.[10] Simply put, in the calculation of ruling in one cause and ruling out others, unusual specificity in the circumstances can make specific causation straightforward.

However, when such specificity is not present—as is typically the situation in toxic-tort cases—the inferential task of reasoning from general data to a specific case becomes substantially more complex. Despite the seeming overwhelming nature of this task, the following touchstones can help lawyers and judges assess specific causation.

1. Forms of Empirical Proof

This factor refers to the quality and reliability of the research being relied upon. Inferences about specific causation necessarily depend upon the foundation of empirical work that supports general causation. These include clinical trials, epidemiological research, various areas of toxicology, and, increasingly, genetic information. Each of these sources of evidence, however, must be assessed in terms of its internal validity, external validity, and

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[8] References to the criteria appear in over 120 legal opinions on causation. *E.g.*, Gannon v. United States, 571 F. Supp. 2d 615, 624 (E.D. Pa. 2007); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 473–74 (W.D. Pa. 2003).

[9] *See, e.g.*, Heller v. Shaw Indus., Inc., 167 F.3d 146, 154 (3d Cir. 1999).

[10] Betz v. Pneumo Abex, LLC, 44 A.3d 27, 51 (Pa. 2012).

plausibility. An inference of specific causation will be supported more by strong scientific evidence of general causation than by weak scientific evidence of general causation.

This methodological focus raises the question of whether a statistical threshold of relative risk supports inferences of specific causation from general causation. Some courts, for example, view a relative risk greater than 2.0 as sufficient to prove specific causation by a preponderance of the evidence.[11] A statistical threshold has intuitive appeal, but its inferential power is only as good as the foundation it stands on. Evidence of relative risk greater than 2.0 is less persuasive if, for example, only a single study supports it, or the methodologies of supportive studies suffer from significant validity problems, or other bodies of research call into question the plausibility of the inference. In those cases, additional evidence may be needed to justify specific causation.

2. Strength of General Causation Compared to Strength of Alternative Causes

When specific causation cannot be resolved easily through specific circumstances or compelling statistical proof, the resolution of specific causation becomes more complex and more uncertain because of the possibility that an alternative cause may have been the true cause. Under these circumstances, prevalent in toxic-tort cases, specific causation requires comparing the strengths of general causation against the strength of alternative causes. That comparative inquiry implicates the following issues.

a. Adjusting the Relative Risk. When epidemiologic evidence does not by itself indicate 2.0 relative risk, "effect modifiers" may justify adjusting the risk score upward. Biomarkers of susceptibility, for example, may indicate that a particular individual is more sensitive to injury from the exposure than is the average person in existing epidemiologic studies. Or the individual may have been exposed to a larger dose than subjects in the studies. These examples lead to the general point that whenever an individual can be placed within a specific subgroup, calibrating the relative risk for the subgroup leads to a more valid, though less precise, estimate of the relative risk.

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[11] *E.g.*, Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 716 (Tex. 1997).

b. Assessing the Strength of the Effect of Competing Causes. The comparative analysis requires assessing the strengths of competing causes. When multiple risk factors exist, they may combine to produce an overall risk of harm. When possible, courts should ascertain how multiple risk factors interact. When not possible, courts should examine the relative individual strengths of risk factors. Effect modifiers should be considered for each risk factor. Proof of specific causation is made especially difficult when an individual has multiple risk factors and some of them are more strongly correlated with the plaintiff's injury than is the risk under consideration.

c. Idiopathic Causes. Except for signature diseases, some individuals who suffer from a particular injury do so for no discernable reason. For them, the injury is idiopathic. Because an expert cannot scientifically or logically rule out an idiopathic cause, courts should consider disregarding the effect of potential idiopathic causes when they comprise a relatively small percent of the kind of injuries in question. Disregarding idiopathic causes is less reasonable for those injuries, like acute myeloid leukemia, that have idiopathic causes in a substantial majority of cases.[12]

d. Lack of Human Data. Many injuries have no relevant group-level human data. These include injuries resulting from a sporadic accident, circumstances presenting ethical barriers to research, and areas of relatively new research. The lack of relevant human data inevitably makes proof of specific causation more difficult, but many of the Bradford Hill indicia can prove useful. Dosage, similar injuries across several non-human species, and toxicologic evidence indicating a similar pathway of injury are indicia of biological plausibility and specificity. Analogy to other, better-understood causes also modestly strengthens a specific causation argument. It is important, however, not to overstate the ability of this type of evidence to establish specific causation. When there is a substantial lag time between exposure and injury, when the level of the plaintiff's exposure is not especially great and when known competing causes are present, proof of specific causation without relevant human data remains difficult.

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[12] *E.g.*, Milward v. Acuity Specialty Prods. Grp., 639 F.3d 11 (1st Cir. 2011).

e. Individuating Circumstances. High percentages of idiopathic causes, a lack of group-level human data, and significant lapses of time between exposure and the manifestation of injury make it difficult to prove specific causation. In these situations, available biomarkers of illness and exposure may help strengthen or weaken the proffered cause or competing causes. Evidence of a biological gradient may strengthen specific causation for individuals exposed to particularly high doses. In general, the Bradford Hill indicia help point the way toward developing individuating information about a person.

Conclusion

This chapter aims to supply lawyers and courts with scientifically grounded tools for useful and reliable differential etiology. At the very least, I hope it will encourage courts to clearly articulate the types of information upon which differential-etiology judgments should be based.

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