General Causation Analysis

The Abuse of Biological Plausibility as a Factor

By Eric Swan and Jon Strongman

[T]he most fundamental error a scientist can make is to mistake the hypothesis for an explanation of a phenomenon without having performed any experimental tests.

Patricia Gosling & Bart Noordam, Mastering Your PhD: Survival and Success in the Doctoral Years and Beyond, Springer Publishing 29 (2d ed. 2011).

In 1993 the U.S. Supreme Court issued the landmark decision *Daubert v. Merrell Dow*, 509 U.S. 579 (1993), to clarify the law governing the admissibility of expert testimony. Twenty years later courts across the country continue to grapple with difficult admissibility determinations, often when adjudicating drug and medical device mass torts with high stakes, where *Daubert* hearings become the functional equivalent of trials.

Despite years of developing case law, the criteria for determining the admissibility of expert testimony remain unclear, not to mention highly variable depending on the jurisdiction. Is epidemiology required to prove causation? Are case reports sufficient or even admissible? How should courts weigh disparate forms of evidence such as in vitro studies, animal studies, and case series? Should multiple lines of evidence be evaluated independently or considered as an aggregate using a weight-of-the-evidence approach? Courts differ in their answers to these questions, and a full discussion is beyond the scope of this article. Instead, this article focuses on one discrete, problematic development: the overreliance of courts on biologic plausibility as a factor in general causation analysis.

Recent Case Law on Biologic Plausibility

Plaintiffs' lawyers increasingly advance theories of causation that are largely predicated on biologic plausibility. For example, in the Bausch & Lomb litigation, the plaintiffs' attorneys advanced theories of causation that relied almost entirely on "biologically plausible" theories of causation. Although ultimately rejected by both the federal multidistrict litigation court and the court in the New York consolidated action, both of which ruled that the plaintiffs' expert testimony was inadmissible, the Bausch & Lomb litigation stands as a prime example of how plaintiffs' lawyers try to use biological plausibility to press meritless cases. *In the Matter of Bausch & Lomb Contact Lens Solution*

■ Eric Swan is an associate and Jon Strongman is a partner in the Kansas City, Missouri, office of Shook Hardy & Bacon. Mr. Swan he focuses his practice on defending pharmaceutical and medical device product liability claims. He has a bachelor's degree in Chemistry and an M.S. in Cancer and Cellular Biology. Mr. Strongman focuses his practice on defending complex litigation with an emphasis on pharmaceutical and medical device product liability claims. He has experience managing large-scale litigation such as federal multidistrict litigation, as well as individual actions in state and federal courts across the country.

Prod. Liab. Litig., 2009 NY Slip. Op. 52571, 906 N.Y.S.2d 778 (N.Y. Sup. Ct. 2009) ("The plaintiffs originally had seven experts whose mechanism of action hypotheses fell into the following [six] general categories."); *In re Bausch & Lomb Inc. Contact Lens Solution*, 693 F. Supp. 2d 515 (D. S.C. 2010). Unfortunately, in some cases courts have obliged.

Courts increasingly rely on biologic plausibility as a factor in causal inference. They have cited plausibility as a key consideration in several recent *Daubert* decisions. *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 181 (S.D.N.Y. 2009); *In re Neurontin Mktg.*, 612 F. Supp. 2d 116, 145 (D. Mass. 2009). The court in the Neurontin litigation cited plausibility as "a key factor" influencing the decision to admit the testimony of the plaintiffs' expert: "In addition to lengthy debate over the existence, strength, and specificity of the association, most of the hearing focused on the question of biological plausibility, a key factor in Bradford Hill analysis." *In re Neurontin Mktg.*, 612 F. Supp. 2d at 145. Similarly, the issue arose in the Fosamax litigation. In affirming the reliability of the plaintiffs' experts' methodology, the court noted that both parties had agreed that "the significance of [biologic plausibility] increases when epidemiological evidence is lacking or inconclusive." *In re Fosamax*, 645 F. Supp. 2d at 181. This increasing reliance on biologic plausibility is not only troubling, it is misplaced.

We argue that biologic plausibility is virtually worthless in assessing whether an association is causal. The reasons for this are threefold: (1) it is nothing more than a hypothesis; (2) it is an extremely poor predictor of truth; and (3) it is easily manufactured. However, it can be helpful in one legal way: as an exclusionary criterion. When it is absent, a causal inference should be rejected outright. Aside from this, it is otherwise meaningless. Rather than spend resources focusing on arguments of plausibility, courts should focus instead on the underlying evidence.

Plausibility Gone Wrong—A Modern Example

In 1981, reports of a rare form of pneumonia found only in immunosuppressed patients was published in the June 5, 1981, issue of Morbidity and Mortality Weekly Report. U.S. Ctrs. for Disease Control and Prevention, *Pneumocystis Pneumonia—Los Angeles*, 30(21) Morb. Mortal. Wkly. Rep. 1–3 (June 5, 1981), available at http://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm. Shortly after, multiple cases of a rare form of cancer were identified in men in California and New York. Within three years of these reports, the Human Immunodeficiency Virus (HIV) was identified. That same year "then U.S. Health Secretary Margaret Heckler [] publicly proclaim[ed] at a news conference on April 23, 1984, that a preventive HIV vaccine could be expected to be available for testing within 2 years." Walker B. & Burton D., *Toward an AIDS Vaccine*, 320 Science, 760–64, 760 (May 9, 2008). This assessment turned out to be wildly overoptimistic.

Over the next quarter century, the National Institutes of Health provided support for clinical trials involving 55 different vaccine products. Robert Steinbrook, *One Step Forward, Two Steps Back—Will There Ever Be an AIDS Vaccine?*, 357 N. Engl. J. Med. 2653–55, 2655 (2007). None of them proved effective at preventing HIV infections.

One particularly disappointing trial began in 2005. The STEP study used what was considered the "lead candidate" among T-cell-based HIV vaccines. L. Corey *et al.*, *Post STEP Modifications for Research on HIV Vaccines*, 23(1) AIDS 3–8 (Jan. 2, 2009). In September 2007, just two years after it started, the study was halted when a preliminary analysis showed that the vaccine did not work. Later analysis showed that 49 of 914 men injected with the vaccine developed HIV compared with 33 of 922 who received the placebo. Kyung Song & Carol Ostrom, *Failure of AIDS vaccine punctures soaring hopes*, The Seattle Times, Nov. 8, 2007, http://seattletimes.com/html/health/2004001162_stepvaccine08m.html. Contrary to the hypothesis of the study, not only did the vaccine not protect patients from contracting HIV, it seemed to increase the risk of contracting the virus, although the results were not statistically significant so no conclusions could be drawn.

The inability of the scientific community to develop an effective HIV vaccine despite decades of research and development and billions of dollars of investment has dampened the hopes of many in the scientific community that an HIV vaccine will be developed in the near future. But it is also a cautionary reminder for those placing great emphasis on biologic plausibility in general causation analysis. The HIV epidemic spawned the development of some of the most sophisticated and scientifically tailored vaccine candidates ever developed. Despite the fact that it was biologically plausible that each of those vaccine candidates would induce immunity from HIV, none of them proved effective when actually put to the test. Instead, as of today, "there is neither a marketable vaccine nor a credible expectation about when there will be one." Steinbrook, *supra*, at 2653.

Rather than spend resources focusing on arguments of plausibility, courts should focus instead on the underlying evidence.

Biologic Plausibility—A Synonym for "Hypothesis"

Biologic plausibility is a factor that scientists consider when making causal judgments. Biologic plausibility was most famously identified as a factor in causation analysis by Sir Austin Bradford Hill in his speech of 1964. In what has become known as the Bradford Hill criteria, Hill laid out nine factors to be considered by scientists when trying to confirm whether an observed association is likely causal or not. These include strength of the association, consistency, specificity, temporality, biological gradient, biologic plausibility, coherence, experimental evidence, and analogy. *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965). The Bradford Hill criteria are often cited by courts as a model for causal inference.

Courts addressing biologic plausibility almost uniformly define it as "a judgment about whether an agent plausibly could cause a disease, based on existing

knowledge about human biology and disease pathology." *In re Fosamax Products Liability Litigation*, 645 F. Supp. 2d at 181 (citing Michael D. Green *et al.*, Reference Guide on Epidemiology 388, *in* Fed. Jud. Ctr., Reference Manual on Scientific Evidence (2d ed. 2000)). *See also Milward v. Acuity Specialty Prods. Group*, 639 F.3d 11, 25 (1st Cir. 2011). Courts adopt this definition with little or no discussion about whether it accurately reflects the scientific use of the term. In fact, one scientific review paper identified three separate definitions for biologic plausibility ranging from an "evidence-free" approach, in which "a reasonable mechanism can be hypothesized, but for which no biologic evidence may exist," to an "evidence-supportive approach," and finally, a much more rigorous approach requiring "sufficient evidence to show how the factor influences a known disease mechanism." D. Weed & S. Hursting, *Biologic Plausibility in Causal Inference: Current Method and Practice*, 147(5) Am. J. of Epidemiology, 415–25, 416–17 (Mar. 1, 1998).

Once a plaintiff's attorney has articulated biologic plausibility, a court should then evaluate the underlying data to determine how strongly it supports a causal inference.

Courts that discuss biologic plausibility almost universally apply a weak form of the middle definition, an "evidence-supportive approach." Indeed, it is the only legitimate definition of biologic plausibility. An evidence-free approach makes no sense. All theories presuppose consistency with some basic preexisting knowledge; otherwise no one would theorize them. Similarly, it makes no sense to call the latter definition biologic *plausibility*. If you can show how a factor influences a known disease mechanism, the theory is no longer a plausibility. It is an actuality. This leaves only the evidence-supportive approach. Under this approach, biologic plausibility is the equivalent of a hypothesis or an educated guess.

Plausibility Is a Poor Indicator of Truth

The biggest problem with overemphasizing biologic plausibility is that plausibility is a poor predictor of truth. Biologic plausibility is nothing more than a theory—a hypothesis—and most hypotheses turn out to be wrong. Indeed, every day, in thousands of research labs across the county, scientists test plausible theories. If they were not plausible, no one would be testing them. Most of these fail.

Consider a study conducted by Kevin Dunbar, a researcher who studies how science operates. He followed four Stanford University biochemistry labs for a year to see how science is conducted in the real world. Much to his surprise he found that

> more than 50 percent of their data was unexpected. (In some labs, the figure exceeded 75 percent.) 'The scientists had these elaborate theories about what was supposed to happen,... [b]ut the results kept contradicting their theories.' It wasn't uncommon for someone to spend a month on a project and then just discard all their data because the data didn't make sense.

Jonah Lehrer, *Accept Defeat: The Neuroscience of Screwing Up*, WIRED Magazine, Dec. 21, 2009, http://www.wired.com/magazine/2009/12/fail_accept_defeat/all/1.

Anyone who has conducted basic science research can sympathize with this frustration.

Drug approvals are another good example. Research indicates that only 11 percent of drugs that enter Phase I testing ever gain approval. I. Kola & J. Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 Nature Rev. Drug Discov. 711N715, 711 (2004). Before companies begin human testing they conduct preclinical testing (*i.e.*, test tube and animal studies) to select the most promising compounds. These promising compounds will have demonstrated efficacy in preclinical testing. This means that 89 percent of the most promising, heavily studied, biologically plausible compounds fail to pan out once they reach the clinical stage.

Cancer research has fared little better. Although there are some wonderful and obvious success stories—the ability of GLEEVEC (imatinib), a pill with minimal side effects, to induce complete remissions of chronic myelogenous leukemia in 95 percent of patients—the overall picture has not changed much since President Nixon declared war on cancer in 1971. S.G. O'Brien *et al.*, *Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia*, 348 N. Engl. J. Med., 994–1004 (2003). *See* Clifton Leaf, *Why We're Losing the War on Cancer [And How to Win It]*, Fortune Magazine (Mar. 22, 2004). Time and time again, therapies that appear very effective in animals fail in humans. This theme is echoed in the statement of Richard Klausner, the former head of the National Cancer Institute: "The history of cancer research has been a history of curing cancer in the mouse... We have cured mice of cancer for decades—and it simply didn't work in humans." M. Cimons, J. Getlin, & T. Maugh II, *Cancer Drugs Face Long Road from Mice to Men*, L.A. Times, May 6, 1998, http://articles.latimes.com/1998/may/06/news/mn-46795.

Plausible Explanations Are Everywhere

Another problem with overemphasizing biologic plausibility is that it will almost always exist because it is easily manufactured. It is easily manufactured because plausibility can be defined at almost any level of abstraction. A few hypotheticals will help illustrate the point.

Imagine a case in which the plaintiff claims that an industrial chemical causes lung cancer based on multiple lines of evidence: (1) it's highly volatile (*i.e.*, it releases a lot of fumes), and so can be readily inhaled in the lungs; (2) animal studies show that it causes lung cancer in mice when applied *to the skin*; and (3) it is known to cause DNA damage in laboratory cell lines. Based on this information, it is at least conceivable that the chemical causes lung cancer in humans. In this scenario, the chemical has been shown to cause DNA damage in lab tests, a potentially carcinogenic property. It has also been shown to be capable of causing lung cancer in animal studies. And finally, its high volatility

provides a plausible mechanism for delivery into the lungs. Taken together, you have a biologically plausible theory. Now let us change the facts.

This time the second fact disappears, leaving only the volatility and laboratory studies showing that the chemical can cause DNA damage. Still, under these circumstances, it is arguably plausible that it causes lung cancer. Again, we know that it can cause mutations in the DNA, which is a hallmark of many other carcinogens, and we know that it can be delivered to the lungs through inhalation.

This time let us change the facts more. Only the first fact remains—its high volatility. But this time there is additional evidence that "structurally similar" compounds have been shown to cause DNA damage in lab studies and cause cancer in animals. Again, under these circumstances it's arguably plausible that the chemical causes lung cancer in humans. Similar compounds often have similar properties, and the fact that the similar compound causes some form of cancer in animals suggests that the chemical may be a human carcinogen.

The above hypotheticals illustrate a key problem with biologic plausibility: There is no limit to the degree of abstraction at which it can be articulated. If you don't have human data, use animal testing. If you don't have animal testing, use in vitro testing. And if you don't have those, analogize it to other compounds for which you do have testing. At each increasing level of abstraction the data becomes weaker and yet "plausibility" remains.

This may sound a little farfetched, but it is not. It is precisely what happened in *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672 (M.D.N.C. 2003). In *Dunn*, the plaintiff asserted that Parlodel, a drug used to prevent post-partum lactation, among other things, caused her to suffer a stroke. The defendant challenged the scientific evidence linking Parlodel to stroke as unreliable. The parties agreed that there was no definitive epidemiologic evidence. Nevertheless, the plaintiff pointed to studies conducted using drugs with "similar molecular structures." Structurally similar compounds called ergots had been shown to cause vasospasms, which were linked to risk of stroke. The plaintiff argued in essence, that Parlodel is an ergot alkaloid, ergot alkaloids cause vasospasm, and therefore, Parlodel causes vasospasms. Hence, the plaintiff constructed a biologically plausible argument based upon testing done on completely different compounds.

Moreover, plausibility is even easier to manufacture today than it was a century ago. The reason for this is simple: We know a lot more now than we did then. This increased knowledge makes it easier to hypothesize plausible explanations for observed associations. Although not directly addressed by Hill, his discussion of analogy, the ninth factor in his list, contains the kernel of this idea: "Analogy: In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy." Hill, *supra*, at 299. Hill was making the point that once we have evidence of a causal connection between one disease and an outcome, that connection gives us greater confidence that similar observations are likely causal. But another point salient to plausibility is contained in his analysis; namely, once a causal relationship between an exposure and a disease is identified, it becomes easier to hypothesize plausible explanations for other relationships.

For example, once the first microorganism was identified as a cause of human disease, it became much easier for scientists to ascribe a plausible explanation to other disease (*i.e.*, they are caused by different microbes). As our scientific knowledge expands so too does the availability of plausible explanations for observed associations. Today, with our greatly expanded knowledge of toxicology, cell biology, and molecular biology we have greater wealth of knowledge from which to draw plausible explanations.

Where Do We Go from Here?

Biological plausibility does have a place in tort law, but courts should rethink that place.

Biologic Plausibility—An Exclusionary Criterion

In tort law, biologic plausibility is most useful as an exclusionary criterion: Biologic plausibility should be required, but its existence is otherwise minimally relevant. To understand this, it is helpful to imagine a case in which there was no biologic plausibility. In this hypothetical case, the plaintiff would have to file a case alleging that a product caused an injury even though there is no conceivably rational explanation for how it could happen. A case with no biologic plausibility is equivalent to an observation with no hypothesis. It is the starting point of science, not the end.

As eloquently stated by Judge Posner, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it."

Plausibility Is Not Evidence

Once a plaintiff's attorney has articulated biologic plausibility, a court should then evaluate the underlying data to determine how strongly it supports a causal inference. This concept is touched on in the Restatement (Third) of Torts: "[The strength of biological-mechanism evidence] may vary from quite compelling to no more than hypothesis, with little supporting the latter other than some biologic knowledge and a fertile imagination." Restatement (Third) of Torts §28, Reporters Note, cmt. c. While there is some truth to the notion that "there is no methodology for assessing the strength or reliability of biological-mechanism evidence," we do have scientifically valid criteria to apply. Some examples would include the following:

- Has the substance been shown to produce the same disease in animals?
- Is the injury produced in animals identical to that in humans, or is it something less?
- Have those animal models been shown to be good predictors of similar diseases in humans?
- Is the plausibility based on analogies to "similar compounds," which is virtu-

ally worthless, or have they been demonstrated with the identical compound?
- Can you identify markers of the predicted effect in humans?
- Was the plausibility, or the expected effect, predicted before the outcome was ever observed?

In this way, the focus is less about the existence of "plausibility" and more about the strength of the actual evidence.

Reconciling Bradford Hill with the Requirement of Biologic Plausibility

We need to address one last closing point relevant to biologic plausibility in tort law. Requiring biologic plausibility is seemingly at odds with Hill's own conclusions on the issue. Rather than demanding biologic plausibility, Hill stated, "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biologic knowledge of the day." *Hill, supra*, at 298. "Convinced we cannot demand" implies that biologic plausibility is a high threshold, which is often unattainable. How can we reconcile our demand for biologic plausibility in a legal context with Hill's admonition that it is something that science cannot demand? There are two answers to this apparent paradox.

First, law and science have different functions and operate with different constraints. The function of law is to make final binding judgments to resolve disputes at specific points in time. In contrast, science has no such time constraints. Science proceeds by the scientific method: A continual process of hypothesis, testing, and reformulation that continues indefinitely as theories are tested, rejected, and refined. Science has the benefit of time to supply answers that the law does not. This concept was discussed by the Supreme Court in *Daubert*:

> It is true that open debate is an essential part of both legal and scientific analyses. Yet there are important differences between the quest for truth in the courtroom and the quest for truth in the laboratory. Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly. The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance. Conjectures that are probably wrong are of little use, however, in the project of reaching a quick, final, and binding legal judgment—often of great consequence—about a particular set of events in the past. We recognize that, in practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will prevent the jury from learning of authentic insights and innovations. That, nevertheless, is the balance that is struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes.

Daubert, 509 U.S. at 596–97. *See also Moore v. Ashland Chem., Inc.*, 151 F. 3d 269, 276 (5th Cir. 1998) ("[T]he law cannot wait for future scientific investigation and research. We must resolve cases in our courts on the basis of scientific knowledge that is currently available."). Law cannot supply answers that science has not. As eloquently stated by Judge Posner, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

Second, Hill's statement about biologic plausibility is correct—in the right context—and could serve as an exception to the legal requirement of biologic plausibility if courts applied his criteria correctly. Unfortunately, they often do not. By Hill's own admission, before applying his criteria, scientists first must identify a "perfectly clear-cut" epidemiologic association between an exposure and an outcome. *Hill, supra,* at 295. The law frequently has misapplied this scientific methodology by reversing the methodological steps. An epidemiologic study was the starting point for his analysis. *Soldo* v. *Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 514 (W.D. Pa. 2003). Without an observed association using the Bradford Hill factors "to provide the sole basis for proof of general causation does not reflect accepted epidemiologic methodology." Restatement (Third) of Torts: Physical & Emotional Harm, §28, Reporter's Note, cmt. c (2010); *accord Dunn*, 275 F. Supp. 2d at 678. In contrast, courts have applied the Bradford Hill criteria even in cases when no epidemiologic studies existed. *See, e.g., Milward*, 639 F.3d 11 (no statistically significant epidemiology). Indeed, most courts explicitly state that plaintiffs do not need to proffer epidemiologic studies to prove causation. *Id.* at 24; *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986 (8th Cir. 2001).

If courts applied the Bradford Hill criteria correctly, and required a strong epidemiologic association, they might not require biologic plausibility or resort to requiring it. If plaintiffs met many of the other Bradford Hill criteria, meeting them might justify drawing a causal inference even if no plausible explanation could be had.

However, in practice, this scenario will almost never occur. Someone would have to ask who funded an epidemiologic study to look for an association that was, based on current scientific knowledge, implausible. Except for a few notable examples from the past, most of which come from the time when doctors still used leaches to bleed patients, we have few modern examples of associations for which no plausible explanation could be given. The reason for this is simple: Plausible explanations are nothing more than hypotheses, and hypotheses, though the appropriate starting point for legitimate science that can lead to beneficial scientific discoveries, are easily manufactured.

Conclusion

Anyone who has conducted basic science research can tell you that science is an incredibly frustrating profession, one fraught with repeated failures and discarded theories. Sometimes theories turn out to be not just wrong, but strikingly wrong, as was the case with HIV vaccine tested in the STEP trial. A vaccine that was intended to prevent HIV infections may have actually increased the risk of contracting the disease. Judges increasingly face scientific theories far less sound than the theory that supported the HIV vaccine in STEP, and the dozens of other failed HIV vaccine candidates. They would be wise to look with great suspicion on thinly supported but biologically plausible theories. The graveyard of science is littered with these. FD