The *Daubert* Hearing: From All the Critical Perspectives

Hypothetical

In 1895 Professor David Sole at the University of Wisconsin Medical School identified the infamous foot disease that now bears his name. Patients with Sole's Foot suffer constant and chronic pain on the bottoms of their feet, which they describe as blister-like without the blisters. It is a neurological disorder. A study conducted in 2005 estimated that every year about five of every 100,000 people develop Sole's Foot, and that overall about 200,000 people in the United States were then living with it. The disease occurs with equal frequency among men and women, and usually develops between the ages of thirty and fifty. The cause is not known.

Until 2008 the only treatments were various ointments that dulled the pain but did not eliminate it. Then in January 2008 the Alpha-Toe Pharmaceutical Company began marketing a drug called AlphaSoleCure that made the symptoms essentially disappear. The recommended prescription was one ten mg dose, injected once a month. Despite its name, AlphaSoleCure was not really a cure, but a very effective treatment if taken regularly. If a patient went off the drug, however, the disease would return.

In three clinical trials, each six months long, more than ninety percent of patients in the drug arms reported complete remission, and all but a few patients reported at least some improvement. The only adverse effects reported were occasional dry mouth for a day or two after taking the drug, some intestinal problems, and a few instances of liver enzyme abnormalities. One patient in one of the studies developed blurred vision, but there was no ophthalmology investigation and no other ophthalmologic adverse events. The relevant results from the studies are shown in Table 1.

In January 2009 the Beta-Toe Pharmaceutical Company and the Gamma-Toe Pharmaceutical Company began marketing drugs similar to AlphaSoleCure, but different enough to avoid patent infringement

claims. BetaSoleCure and GammaSoleCure were also taken monthly, and had to be continued or the symptoms would return, but both had the advantage of oral administration. The dose for BetaSoleCure was 500 mg; for GammaSoleCure it was 1200 mg. By 2010, well more than half the patients with Sole's Foot were on one of the drugs, all of which were polystatols that inhibited an enzyme known to be related to nerve function.

Table 1. AlphaSoleCure Clinical Trials

	Alpha Study 1	**Alpha Study 2**	**Alpha Study 3**	**Total**
Number in Drug Arm (DA)	1,205	505	950	2,660
Remissions in DA	1,084	456	881	2,421
Improvement in DA	115	45	62	222
Total Adverse Events in DA	850	400	677	1,927
Ophthalmologic Adverse Events in DA	0	0	1	1
Number in Placebo Arm (PA)	1,202	510	948	2,660
Remission in PA	15	4	8	27
Improvement in PA	50	12	30	92
Total Adverse Events in PA	628	349	507	1,484
Ophthalmologic Adverse Events in PA	0	0	0	0

It was generally understood that the enzyme in question had no role in pain sensitivity except in the skin. For BetaSoleCure there were two non-specific ophthalmologic adverse events in one of two clinical trials. For GammaSoleCure, there were a total of ten ophthalmologic adverse events in two clinical trials. The results for the BetaSoleCure trials are shown in Table 2, and the results for the GammaSoleCure trials are shown in Table 3. Like the AlphaSoleCure trials, all these trials ran for six months.

Table 2. BetaSoleCure Clinical Trials

	Beta Study 1	**Beta Study 2**	**Total**
Number in Drug Arm	660	920	1,580
Remissions in DA	546	790	1,336
Improvement in DA	95	110	205
Total Adverse Events in DA	750	800	1,550
Ophthalmologic Adverse Events in DA	0	2	2
Number in Placebo Arm	650	925	1,575
Remission in PA	15	4	19
Improvement in PA	50	12	62
Total Adverse Events in PA	628	349	977
Ophthalmologic Adverse Events in PA	0	0	0

Table 3. GammaSoleCure Clinical Trials

	Gamma Study 1	**Gamma Study 2**	**Total**
Number in Drug Arm	525	400	925
Remissions in DA	400	312	712
Improvement in DA	45	31	76
Total Adverse Events in DA	601	465	1,066
Ophthalmologic Adverse Events in DA	6	4	10
Number in Placebo Arm	520	499	1,019
Remission in PA	4	2	6
Improvement in PA	15	12	
Total Adverse Events in PA	250	199	449
Ophthalmologic Adverse Events in PA	0	0	0

All seemed much improved and well in the Sole's Foot world until March 2010, when eye doctors began reporting a sudden increase in a previously very rare disorder of the optic nerve known as photoneuritis, or Red Dot Syndrome. People with this disease have their vision obscured by what look like large red polka dots. It is irreversible once it develops. Before 2010 there were a total of twenty-five cases reported in the literature since 1900, but there were fifty case reports for 2010 alone, half of which did not mention a polystatol drug.

Meanwhile the Gamma-Toe Pharmaceutical Company had received seventy-five adverse event reports for Red Dot syndrome since

GammaSoleCure went on the market. To be clear, that's seventy-five reports during the first fifteen months the drug was on the market. Alpha-Toe and Beta-Toe also received such case reports, but in smaller numbers. The annual number of doses for each drug and the number of case reports received are shown in Table 4.

Table 4. Photoneuritis Adverse Event Reports By Year and Drug

Year	Doses of Alpha	Alpha Photoneur-itis Reports	Doses of Beta	Beta Photoneur-itis Reports	Doses of Gamma	Gamma Photoneur-itis Reports
2008	300,000	7				
2009	700,000	19	100,000	9	120,000	65
2010	750,000	32	200,000	35	200,000	170

The breakdown of the case reports by number of doses before onset is shown in Table 5. Most reported adverse events occurred while the patient was still taking the drug in question, though there have been a few reports for all three drugs of cases occurring as much as five months after cessation of therapy.

Table 5. Doses Before Onset of Red Dot Syndrome

No. of Doses Before Onset of Disease in Adverse Event Reports	Alpha	Beta	Gamma
1	0	1	4
2	1	0	10
3	0	1	16
4	2	2	20
5	4	3	25
6	5	5	30
7	7	7	35
8	8	6	31

9	10	8	29
10	10	8	27
More Than 10	11	3	8
TOTAL REPORTS	58	44	235
TOTAL DOSES	1,750,000	300,000	320,000
Reports per 100K Doses	3.31	14.66	73.43

Plaintiffs' lawyers immediately jumped on this data and rushed to file cases seeking multi-district litigation status for the polystatol drugs and perhaps class certification. Twenty different firms filed cases, and each began jockeying to be designated lead counsel for an MDL in its home Federal District.

None of the drug companies initiated any new investigation of a possible link between polystatols and Red Dot Syndrome, but Alpha-Toe Pharmaceuticals did convene a panel to review all the medical records from its clinical trials to determine if, in retrospect, there had been cases of photoneuritis. The diagnostic criteria for the disease were not part of the original study protocols, so they looked for other symptoms sometimes associated with photoneuritis. The review was difficult and imprecise, but the panel found ten possible cases in the drug arms and one case in the placebo arms.

The FDA took no action until January 2011, when a Chicago ophthalmologist named Victor Vishun published a paper in *Seeing Eye Journal*. It reported on forty cases of photoneuritis (all in his patients) and noted that every single one of the patients was taking a polystatol drug. Ten were taking AlphaSoleCure (all after three or more doses), eight were taking BetaSoleCure (one after three doses, one after four doses, three after five or more doses, and three after an indeterminate number of doses), and twenty-two were taking GammaSoleCure (one after a single dose, two after two doses, two after three doses, five after four doses, and the rest after five or more doses). With the publication of this article the FDA convened an expert panel that recommended addition of a black box warning to the labels for all polystatol drugs, but the three pharmaceutical companies resisted and negotiated for a much milder label change that included only precautionary language.

Gamma-Toe in particular was vigorous in its defense of polystatols, and it gave a grant to Perry Eyefell, a famous professor of Ophthalmology at Shortsight University to go back and review thousands of blurred vision case reports and studies to show that

photoneuritis was really much more common than previously believed. His article appeared in the December 2010 issue of *Blind Eye Journal*, which did not require disclosure of his relationship with the drug company. It claimed that instead of twenty-five cases since 1900, there more likely were hundreds of cases, almost all of which predated the polystatols.

Professor Eyefell made no effort to check with the authors of the fifty case reports from 2010 to determine if the patients had in fact been taking a polystatol, but authors of fourteen of the twenty-five reports that did not mention these drugs went back on their own to double check. In every instance the patient had either been taking one of them or at least suffered from Sole's Foot, which would suggest they likely were taking one. The data were insufficient to determine number of doses before onset in most of thirty-nine total case reports that identified a polystatol drug.

Infuriated at what he saw as a distortion of the record, and goaded on by the plaintiffs' lawyers who retained him as an expert witness, Dr. Vishun wrote a scathing letter to *Blind Eye Journal* in which he explained how the enzyme inhibited by the polystatols was in fact involved in the functioning of the optic nerve and why it should have been anticipated all along that these drugs, by inhibiting it, might affect vision. The letter was not peer reviewed. It is generally believed, but not well established, that inhibition of the enzyme is reversible. That is, cessation of a drug that causes inhibition should mean restoration of the body's ability to produce the enzyme. How such a relationship might square with the irreversible nature of photoneuritis was not explained.

The litigation eventually was put into three MDLs, one for each drug. The AlphaSoleCure litigation is now in the District of Davis, California, but there are several cases in this MDL in which a plaintiff actually took more than one of the polystatols, and the judge has asked for expert reports and briefing in one of these cases, involving a forty-year-old plaintiff named John Schuman. After an exchange of expert reports and expert depositions, each side filed a Daubert motion to exclude the other side's experts. These motions focused on two closely related litigation issues: (1) does AlphaSoleCure cause photoneuritis; (2) if so, in a patient who was on AlphaSoleCure for eight months in 2008 (eight doses), then switched to GammaSoleCure in January 2009 and developed photoneuritis a week after taking his third dose, was the AlphaSoleCure a substantial contributing factor to his disease.

The court has decided to hold a hearing at which one expert from each side will testify. Dr. Sander Greenland, an epidemiologist

retained by the plaintiff, has submitted a report in which he opines as follows:

> General Scientific Opinions
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> - Science in general, and epidemiology in particular, can never establish a causal relationship with absolute certainty. The best science can do is determine the likelihood that a hypothesized cause leads to an effect; for example, that a drug causes an adverse event. Moreover, the determination of causality, even in this probabilistic sense, cannot be reduced to a checklist of criteria. Reference 1, Rothman & Greenland, *Causation and Causal Inference in Epidemiology*, 95 American Journal of Public Health S144 (Supp. 1, 2005).
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> - To assess the validity and reliability of a causal inference, the focus should be on whether an empirically supported rational explanation has been provided and on the relative strength of the evidence supporting reasonable alternative explanations.
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> - Epidemiologists typically focus their causal analysis on circumstances in which there is a statistical association. In the context of drugs and adverse events, if an adverse event occurs with greater frequency in patients taking a drug than in similar patients not taking the drug, we say there is a positive association. Typically, association is quantified by measures like relative risk and attributable fraction.
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> - Assigning high probability to a causal relationship does not always require a quantified measure of association. When a previously rare condition starts appearing with much greater than historical frequency, and the vast majority of cases are occurring in people taking a certain drug, it sometimes is not difficult to conclude that, far more likely than not, the drug causes the adverse effect. There are several well-known examples in the literature: (1) thalidomide and phocomelia (Reference 2, Taussig, *A Study of the German Outbreak of Phocomelia*, 180 Journal of the American Medical Association 1106 (1962) (describing circumstantial evidence as overwhelming); (2) suprofen and flank pain syndrome (Reference 3, Rossi et al, *The Importance of Adverse Reaction Reporting by Physicians:*

Suprofen and the Flank Pain Syndrome, 259 Journal of the American Medical Association 1203 (1988) (adverse event reports alone generated an unequivocal signal and established causality with reasonable certainty); cisapride and cardiac arrhtythmia (Reference 4, Perrio, Voss & Shakir, *Application of the Bradford Hill Criteria to Assess the Causality of Cisapride-Induced Arrhythmia: A Model for Assessing Causal Association in Pharmacovigilance*, 30 Drug Safety 334 (2007).

General Causation and Case Specific Opinions

- It appears to me more probable than not that polystatols cause photoneuritis, and that if a patient taking a polystatol develops the disease, it appears to me more probable than not that the drug caused it, no matter which of the polystatols he or she was taking.
- In a patient who has taken more than one of the polystatols prior to developing photoneuritis, it is not possible to separate the drugs for purposes of causal attribution, and in such a patient all polystatols taken could be contributory causes of the disease.
- Thus, in the case of Mr. Schuman, it appears to me more probable than not that both AlphaSoleCure and GammaSoleCure contributed to the causation of his photoneuritis.

Dr. William A. Toscano, an expert in environmental health sciences retained by the defendant, has submitted a report in which he concluded:

General Causation Opinions — A Case of Flawed Evidence

Mechanism

- There is a general scientific consensus that we do not know the causal mechanism for photoneuritis, so we cannot directly infer that AlphaSoleCure or any other polystatol has any significant potential for causing the illness.
- The only postulated mechanism (by Dr. Vishun) is that polystatols can affect an enzyme known to be related to nerve function. But that is a far cry from saying it affects

an enzyme that is involved with sight in any way, or with photoneuritis in particular.

- Indeed, the limited data available actually contradicts Dr. Vishun's postulated mechanism. The fact that photoneuritis does not cease when patients stop taking polystatols strongly suggests that these drugs are not responsible.
- The significantly different rates of photoneuritis associated with the three different polystatols also suggests that every polystatol, pure and simply, may not be involved. Why would the results be so different if polystatols were the cause?

Statistics

- As scientists, we are sometimes prepared to accept epidemiologic studies as sufficient proof that a substance causes a particular disease. Here, however, there is no epidemiological study at all, let alone one establishing that exposure to a polystatol doubles the risk of photoneuritis in any group at any exposure level. This is one of the basically accepted scientific criteria for accepting epidemiologic evidence as sufficient to establish causation. Here all we have are rather non-specific case reports, many of which have not been peer-reviewed.
- This is a case of unquantified correlations, and there's no particular reason to think they mean anything even if they were quantified. To illustrate this point, there is a very good correlation between car sales and the birth rate of children, but no one would contend that buying cars causes pregnancies. What is going on is that car buying correlates very highly with a prosperous economy. The better the economy the more people want to buy cars and have children.
- If, in fact, there has been an actual dramatic increase in the number of cases of photoneuritis in the last few years (something we do not actually know at this point, given the absence of a controlled study of the occurrence of the disease over time), how do we know that it is not due to

something else that has changed over the same period of time?

- What we have here may be nothing more than a random association, which is why we need to apply statistical analyses to make sure that the patterns we may be seeing could not be occurring just by chance. This is where statistical significance and confidence intervals come into play in well-designed and executed epidemiological studies.

- The incidence rates of photoneuritis in the studies we have so far are small for all three drugs, and also quite varied. That means any estimate of incidence must have a wide error band, and I have yet to see anything to indicate that the results are actually statistically significant (i.e., that we can tell whether the differences between the rates in the studies indicate real differences between people taking these drugs and the background rate due to independent causes). I do not rely on the review conducted by Professor Eyefell, but his article in the *Blind Eye Journal* is certainly consistent with causes other than polystatols for photoneuritis.

- Though I understand the plaintiffs have suggested the data in this case is much like the data for Thalidomide and birth defects, that is not right. Birth defects from Thalidomide had a very striking, very high incidence rate. They were quickly pinpointed to exposure during a particular point in the gestation period. There was no question about ambiguity in reporting or diagnosis — unlike here, where some of the literature is non-peer-reviewed reporting by a single physician whose results have not been replicated. Moreover there are significant unanswered questions about his methodology.

FDA Labeling Does Not Support Causation

- A Black Box Warning is required when there is significant risk of serious harm. The FDA may require such a warning even when causation has not been established.

Specific Causation of Mr. Schuman's Photoneuritis

- Even if we assume that polystatols do cause photoneuritis, in the case of Mr. Schuman it cannot be said that AlphaSoleCure more likely than not caused his disease.
- We don't know the mechanism, so we don't know if one dose causes the disease or if it takes several doses. Either way, risk would go up with the number of doses. Suppose there was a toy boat at which someone fires lead pellets from a toy cannon. The boat sinks. Is that because one pellet punctured its hull (the more that are fired, the more likely at least one will score a hit) or because enough pellets landed on the boat to weigh it down? The distinction is important. If the former type of causation applies to polystatols, then earlier treatment with AlphaSoleCure could not be the cause, only subsequent treatment with GammaSoleCure.
- Here, everyone concedes that we do not know what the biological process is that leads polystatols to cause photoneuritis. And that means the most science can say is whether one drug or the other led to more than half the plaintiff's risk of disease. Moreover, given the available data, it is clear AlphaSoleCure was very likely *not* the cause.
- AlphaSoleCure creates a much lower risk of photoneuritis per dose than either of the other two polystatols. GammaSoleCure is generally more than twenty-eight times more likely to cause photoneuritis that AlphaSoleCure. That is a striking difference.
- Even allowing for the fact that Mr. Schuman took AlphaSoleCure for eight months and GammaSoleCure for three months, the latter is still more likely than not the cause. It would still be more than six times more likely to cause the disease than AlphaSoleCure.
- Further supporting my opinion that if any polystatol caused Mr. Schuman's disease it had to be the GammaSoleCure, I note that there is almost no evidence of the disease developing three months after cessation of polystatol use, and that is how long Mr. Schuman was off AlphaSoleCure before his disease developed.

- As to whether the Alpha-Toe re-evaluation of the data from its clinical trials suggests a higher risk with AlphaSoleCure, the answer is yes, but that does not change my opinion that of the two polystatols Mr. Schuman took, GammaSoleCure was far more likely than not the cause. We don't know what would happen if the data from the clinical trials for the other drugs were similarly re-evaluated, but even putting that aside, the AlphaSoleCure risk is still three times lower than the GammaSoleCure risk.
- Even if AlphaSoleCure and GammaSoleCure were both "sufficient" to cause Mr. Schuman's photoneuritis, that does not change my opinion. The terms "contributory cause" or "substantial contributing factor" used by some of the Plaintiff's experts in this case are not scientific terms, and an opinion expressed using such language has no scientific meaning.