Transcript

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LAW SCHOOL
LAW REVIEW

DAUBERT HEARING SYMPOSIUM

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Reported by: BARBARA A. COMO
CSR No. 5794

In re: DAUBERT SYMPOSIUM, March 2, 2012, Davis, CA

APPEARANCES

THE COURT:
HONORABLE JAMES ROSENBAUM
Retired U.S. District Court Judge

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EXPERT WITNESSES:

For the Plaintiff:
Dr. Sander Greenland
Professor of Epidemiology and Professor of Statistics at UCLA

For the Defendant:
Dr. William Toscano
Professor and Division Head Environmental Health Sciences at the University of Minnesota, School of Public Health

Professor Edward Imwinkelried
Professor David Faigman

In re: DAUBERT SYMPOSIUM, March 2, 2012, Davis, CA

EXAMINATION PAGE

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In re: DAUBERT SYMPOSIUM, March 2, 2012, Davis, CA

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BE IT REMEMBERED on Friday, the 2nd day of March, 2012, commencing at the hour of 9:35 a.m., at University of Davis, School of Law, Davis, California, before me, BARBARA A. COMO, a Certified Shorthand Reporter in and for the County of Sacramento, State of California, the following transpired:

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THE COURT: For those of you who are living in the 21st century, not only is this being streamed, but it is the nature of modern scientific law practice that people will tend to look on the Internet. And when they look on the Internet about expert testimony, they may find that these two gentlemen, who are bulletproof experts, may be testifying in ways that would make them very susceptible to cross-examination in other cases. And that actually happens on a daily basis.

This is not canned and scripted, but they have been coached to do things in a way which might not otherwise reflect their extraordinary skill. And so this is the "no harm, no foul" rule being approached.

MR. BLACK: If I might add, your Honor, one of the difficulties in putting together a program like this is that *Daubert* is intended to exclude bad expert testimony. I think we could all agree on that.

And so if you want to have a good illustrative case, you ought to have some bad experts. Well, the people Mr. Smith and I work with generally aren't bad experts.

So I think you will see as the day progresses how we have adjusted to this. We've had to ask the experts to say some things that they not only wouldn't say in a normal courtroom setting because it might be outside their field or scope of their expertise, but also in some cases things with which they actually disagree.

As Judge Rosenbaum has indicated, this is going to be recorded. It's going to be up on the Internet. And should one of our witnesses subsequently testify, we don't want an opposing party to say, "Well, in Davis in 2012 you said this." So that's the reason for the disclaimer.

MR. BLACK: Your Honor, as the Court is aware, both parties in this litigation have proposed to introduce testimony from multiple experts. And there are cross *Daubert* motions that affect all of the experts.

THE COURT: I understand.

MR. BLACK: The Court has requested that each party put on the testimony of one expert in an effort to clarify the expert issues for all of the experts. And so we on the plaintiff's side have decided to put on the testimony of our expert epidemiologist, Dr. Sander Greenland. And Mr. Smith for the defendant, the Alpha-Toe Drug Company, is going to put on as his expert for this proceeding, Dr. William Toscano.

THE COURT: And by agreement, also, the exhibits are admissible unless there is a specific objection, with the understanding that they are also subject to the *Daubert* objection.

MR. BLACK: And, Mr. Smith, if you have anything to add at this point.

Your Honor, with the Court's indulgence as we informed the Court earlier, Professor Greenland was delayed in getting here, and we hope to have him here soon.

THE COURT: Mr. Marshall, would you please go get Dr. Greenland?

Why don't we stand in recess.

(Break taken from 9:39 to 9:58.)

THE CLERK: We are again in session.

THE COURT: Counsel.

The lawyers are quite familiar with the vagaries of the United States judiciary. I have done what federal judges do, which is what I want.

And we are flipping the order of our experts and we will proceed with Mr. Smith.

Counsel.

MR. SMITH: Your Honor, Robert Smith for Alpha-Toe Pharmaceutical.

We would like to call to the stand Dr. William Toscano.

WILLIAM TOSCANO, Ph.D.,

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an expert witness herein, called as a witness by the defendant who, being first duly sworn to tell the truth, the whole truth, and nothing but the truth, was examined and testified as follows:

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THE COURT: Sir, would you be good enough to state your name and spell your last name?

THE WITNESS: William Toscano, T-o-s-c-a-n-o.

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DIRECT EXAMINATION BY MR. SMITH

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Dr. Toscano, could you please describe for the Court your present professional position?

A: I am head of the Division of Environmental Health Sciences at the University of Minnesota School of Public Health and head of the Global Health programs at the same school.

MR. SMITH: Let me show you an exhibit.
Your Honor, may I approach the witness?

THE COURT: Yes, and you may as you need.

Q BY MR. SMITH: Dr. Toscano, let me show you what's been marked Defense Exhibit A. Can you tell me what that is?

A: Yes, it's my curriculum vitae.

Q: Doctor, I would like to go through some of your educational and research background, although it's fully laid out in the C.V. for the Court, but just to cover a few of the highlights.
Let me touch briefly on this.
Can you describe your educational background for the Court?

A: I have a bachelor's degree in chemistry and a master's degree in analytical chemistry from Indiana University of Pennsylvania, which is in Indiana, Pennsylvania. And then I proceeded to the University of Illinois, where I studied biochemistry under the late great I.C. Gunsalus, who was a member of the National Academy of Sciences.

And then I went for a post-doc at the University of Washington, Medical School in Pharmacology, for two years.

Q: Could you please share with us some of your professional appointments over the course of your career?

A: Yes, I was hired at the Harvard School of Public Health in the Toxicology program in the Department of Physiology, which was a new program. And at that time they were looking for somebody who had worked with an enzyme called Cytochrome P450, an enzyme that metabolizes drugs and environmental agents, and also knew something about a calcium binding protein called Calmodulin.

And I was probably the only person in the world who had that combination. It was just fortuitous. I was there for nine years.

And then I was hired at the University of Minnesota, Division of Occupational and Environmental Health. I stayed there for four years and then became Chair of the Department of Environmental Health Sciences at the Tulane School of Public Health and Tropical Medicine.

Then I was recruited back to Minnesota to become Chair of the Environmental Health Sciences Division.

Q: Is that where you are today?

A: Yes.

Q: Are there other educational institutions where you have held teaching positions related to your training in chemistry, biochemistry and pharmacology?

A: No.

Q: Am I correct from reading your C.V. that among your many honors you were elected a fellow on the American Association in the Advancement of Sciences?

A: Yes.

Q: And then you received the Shuman Award from the University of Minnesota for teaching excellence?

A: Yes.

Q: Can you describe some of the courses that you have taught in your various university positions?

A: I teach toxicology for students who are majoring in environmental health and pharmacology and also to physicians who are trying to learn something about toxicologic agents. I also teach a course in general environmental health which looks at agents in the environment and how they interact with humans to cause disease.

I taught a course called Children's Environmental Health, which looks at in utero exposures to chemicals, drugs, nutrients, and so on, and what effects they may have on children for future disease.

Q: Have you personally conducted research that's been published in peer-reviewed literature?

A: Yes.

Q: I see from your C.V. that you have over 50 such publications. Is that correct?

A: Yes, I think so.

Q: Have you ever served on an editorial board for a scientific publication?

A: Yes, I have. I'm on the editorial board of a journal called *Environmental Toxicology*, another journal called *The International Journal of Public Health and Environmental Science*, and I'm on the board of advisors for the *Law School Journal of Science and Technology* at the University of Minnesota.

Q: Separate from that work, have you also served as a peer-reviewer for articles and other publications?

A: Yes, I have been an ad hoc reviewer for the *Journal of Biological Chemistry*, *Biochemistry*, some of the other top journals, and have served on NIH study sections.

Q: Am I correct that while you were at Tulane you initiated the Molecular Toxicology Graduate Ph.D. program that included use of toxicology, epidemiology, and exposure assessments?

A: Yes, that's true. In that program we try to bring together molecular

biology and molecular science with epidemiology so that we can better understand the process of diseases and the spread of diseases.

Q: Fine, Doctor, if you could briefly describe your present research?

A: Yes, I'm interested in how things in the environment interact with receptors and cell signaling.

So you are standing there. I'm standing here. We're all sitting. Because of the signals going on in our cells that keep things on a regular basis, things are normal. Our physiology keeps everything on an even keel. You know you're hungry because there's a signal that comes.

So what I'm interested in is how signals in the environment, be they drugs, nutrients, or environmental agents, can moderate those actions and alter the signal.

So what we look at are signals from the environment that cause confusion to cells in the body that lead to human disease.

Q: To what extent does your work deal with evaluating the strength and weakness of evidence relating to the effects of chemicals or drugs on biological systems including those of humans?

A: It's directly involved in that. We look at things that are mutagenic and non-mutagenic — causes of chronic conditions in humans.

And our systems are derived from human cells. So we believe, I believe, in fact, that's a good surrogate for looking and understanding the manifestation of disease in humans after some insult, either a bio drug or environmental condition.

Q: Doctor, let me turn now to your opinions in this particular case. And let me ask you if in the course of your preparation for your appearance here today, did you familiarize yourself with the available information about the three drugs that are at issue here?

A: I did.

Q: And did that include evaluation of clinical trial data?

A: Yes, I looked at those data for the report.

Q: Did you also familiarize yourself with Dr. Greenland's report?

A: I did.

Q: And the various publications and literature related to the effects of these drugs, both clinical trial and consideration?

A: I did. Let me say I think that Sander Greenland is well-respected, well-regarded, in the area of causality and causal inference. And in general, he's a known expert that I admire.

In this case, I don't actually agree with his analysis, however.

Q: Doctor, as you know, this hearing is intended to address two separate questions. The first one is whether it's been established that AlphaSoleCure, a drug manufactured by my client, causes photoneuritis.

Lawyers tend to refer to that area of an inquiry as general causation.

In addition, we have a secondary question on whether AlphaSoleCure can be said to have been a substantial contributing factor in the disease experience of Mr. Schuman, who took both AlphaSoleCure and another similar drug.

And we call that the specific causation issue.

Q: Let me ask you whether you formed an opinion as to whether or not it has been scientifically established that AlphaSoleCure actually causes photoneuritis?

A: I have.

Q: Would you share that with us?

A: I don't know that it causes it. I can't rule out that it doesn't cause it.

The numbers of the patients and the controls are very small. So it's very difficult to assign a causal relationship.

In my mind as a biological scientist, it's very difficult to give cause and effect, without a lot more substantial data to say, "Yes, indeed this is true."

Q: I'll come back in a few minutes to have you elaborate a little bit on your evaluation of the data, particularly in this case.

But let me turn preliminarily to the second question. I know you have just said you don't believe that it's been established that AlphaSoleCure causes photoneuritis. So I assume that it's obviously

your opinion that you can't say that it contributed to Mr. Schuman's specific causation?

A: That's true.

Q: What I would like to do in light of that, so that the Court has the full benefit of your insights here, is to ask you to assume for the sake of your testimony here that it has been established that AlphaSoleCure does cause photoneuritis in some individuals.

And I'll ask you if even making that assumption you would be of the opinion that there's sufficient evidence to establish that Mr. Schuman's illness was causally contributed to by AlphaSoleCure?

COURT: We are assuming that it does, that it could be considered a causative agent.

Question is did it cause it in Mr. Schuman's case?

MR. SMITH: Yes.

THE COURT: Okay.

THE WITNESS: Even based on the assumption that it could cause it, we don't have enough data to substantiate that Mr. Schuman's disease was caused by this particular drug at the time of exposure.

Q BY MR. SMITH: Okay, Doctor, I promised earlier to go back to some of the details underlying your opinion on general causation.

So let me ask you, if you could, to elaborate on what you believe to be some of the deficiencies in the data that prevent you from being able to say at this point in time that it actually is causal with respect to the disease photoneuritis.

A: Part of the problem I have with that is that no real mechanism has been established for the biological relevance of a causal pathway.

For example, there was one study that was published that showed that an enzyme was inhibited by the drug, and then after withdrawal of the drug, the enzyme came back and then the disease came.

That's very unusual for even neurological enzymes. For example, if you take things that work with neurotransmitters, these are molecules that are released from a neuron across a synapse to a receptor on the other side. "Okay, I want to shake your hand. I want to sneeze or cough," or so on.

There's a molecule that's released called acetylcholine. And that causes the nerve to react. And it's very fast-acting. It's released. It causes the nerve to react.

After the reaction has taken place, the neurotransmitter is metabolized by an enzyme called acetylcholine esterase, and the nerve goes back to a relaxed state.

So that if you are exposed to some chemicals, environmental chemicals or drugs that inhibit that pathway, they inhibit the enzyme; and the nerve impulse is on for prolonged periods of time. In other words, it cannot cause the lowering of the symptom. Sometimes the inhibitors of the enzyme are "suicide" inhibitors, which are irreversible inhibitors.

And what happens is these neurotransmitters are there acting persistently until the new enzyme is formed.

In this case that didn't happen. So I find it difficult to see that that mechanism has any relevance to what's happening with the drug.

Q: Are there situations where even in the absence of a known mechanism, scientists can conclude based on other evidence that there are cause and effect relationships?

A: That's true. I will say that Thalidomide is a good case where you saw children born without limbs and other malformations, and, in fact, we still don't know the mechanism of its action.

But there were studies showing that common exposure produced a rare disease, and it was immediately found.

I think vaccinations, as Dr. Greenland said in his report, are another issue that we didn't know everything about the mechanism of immunity. But it works.

But now I think we need more scientific evidence in the sense of an epidemiology study that would show conclusively that, in fact, this exposure caused the disease in Mr. Schuman's case.

Q: Let me show you what's been marked as Defense Exhibit B.

Please describe to the Court what this is.

A: Okay, this is an examination of the data from the clinical trial six-month rates of action of Alpha, Beta, Gamma, and a placebo. And the data seemed to indicate that Gamma has a much greater adverse effect than Alpha.

Q: Let me put this on the screen so the Court will have the benefit of it.

Doctor, this is data that you derived from the reports, clinical reports, that are available in the literature now?

A: Yes.

Q: Can you tell me in terms of evaluating whether general causation has been demonstrated, whether you find any significance in the variability of the data here, in terms of the relative adverse rates and in the sample sizes?

A: The sample sizes, I think, are quite small to have a definitive answer. But it seems that if you look at the relative adverse rates, the Gamma is much more toxic than the Alpha would be in these data.

THE COURT: You said it is much more what?

THE WITNESS: Likely to be an agent that causes or has a relationship to the neuro disease.

Q BY MR. SMITH: You are aware from the information you have studied that Alpha was the first chemical drug released to treat the SoleFoot problem, that the Beta and Gamma chemicals were generated by other companies, and that they were able to patent them as having significant enough differences to have them patented as separate entities.

Does the fact that you see this large variability in the relevant adverse rates suggest anything about whether the modes of action of the particular drugs might actually be different, might have different effects?

A: I can't say for sure that they would be different as a therapeutic drug, but obviously from the data they are different in their toxicologic actions.

And you see this oftentimes, what we call structure activity relationship. Some drug can be modified, and it could be more therapeutic — but it also could be more toxic if there is a small modification done with the drug that lacks the specificity of action.

Q: Can you tell us, just in general terms, how or why smaller samples create greater uncertainty as to the significance of the results?

A: Because we don't know about the population base. People are sensitive at different levels. Populations are sensitive to drugs differently even within the population.

That is true though our genome is about 99.9 percent the same. If we took the Judge's genome and my genome, we would be 99 percent the same; but we don't look alike.

But this other 0.1 percent of the genome is important from a point of view of what causes disease and why our population is susceptible to these diseases.

So, for example, if you and I go into a tavern where there are people smoking and I break out in an asthma event and you don't, there's something different about our genome. That 0.1 percent of the genome is regulating differences in sensitivities to different exposures.

So I have genes that may say, "Okay, Bill, you can't hang out in these kinds of environments. The smoke bothers you." You have genes that say, "Okay, it's fine."

But the population is a distribution. So sensitivities in the population could show one person could be affected by this, but in the population bases, it could be very few.

Q BY MR. SMITH: Dr. Greenland, as you know, is going to be testifying later today.

He has, as you have mentioned, a very strong background and a great reputation in the field of epidemiology.

But before he makes his presentation, could you share with us some of the reasoning from a scientific standpoint as to why you often want to have a strong epidemiology database before deciding the patterns, associations, or correlations are actually meaningful, as opposed to being random or chance events?

A: Because as it goes on to larger populations, the denominator sort of levels out the differences with individuals of the population. Therefore, if you have a large study covering many thousands of people, hundreds and thousands of people, you then are able to look at the differences that could be real.

Q: Doctor, let me turn now to the question of specific causation.

Here, of course, Mr. Schulman took Alpha for eight months, stopped using it, next took Beta for three months, and then got photoneuritis. The question is whether one can say that the Alpha in this case contributed in a causal way to that illness.

As we get into that, let me ask you this. You mentioned that we don't know the causal mechanism here. That's something that everybody recognizes has not yet been explained or described.

Are there mechanisms in the biological world, associations with drugs or other causal agents, where each exposure doesn't actually contribute to causation, that you have a more probabilistic event or relationship in terms of the model of how the disease occurs?

THE COURT: Excuse me, counsel, could you try and clarify that just a tad?

Q MR. SMITH: Let me ask you if there's an analogy to this in the science, Doctor.

A: There are instances where there's exposure to an agent and then sometime later you see a response in reaction to another agent. You see this in allergies, for example. Sometimes you can get charged up. Your immune system gets charged up from eating something or being exposed to something. And then later you are exposed to a pollen, and you have an anaphylactic event.

THE COURT: Why don't you explain what an anaphylactic event is.

THE WITNESS: You sort of can't breathe any longer, and you have to take steroids and epinephrine to survive. What happens then in the case of an anaphylactic reaction is a cascade of events in which the cells get turned on and it results in a number of symptoms, sometimes resulting in death.

So cytokines, which are small molecules, peptides that regulate the immune system, start going and things happen. We call it a "Cytokine storm" within the body. And then all of a sudden you get hit with another exposure, and then the adverse event occurs.

You see it sometimes in flus and other kinds of infectious diseases, as well.

Q MR. SMITH: Let me give you a lay analogy and see if it resonates in the scientific community.

Let's assume you had a small boat in the water and you started shooting — you had a gun that shot pellets into the boat. And one mechanism by which the boat might sink is that the boat fills up with pellets and cumulatively they weigh so much they cause the boat to sink. In that kind of situation, at least in the lay world, one might say each of the pellets contributed to the sinking of the boat.

But another possible way that it might sink is that most of the pellets don't penetrate the bottom but on a random basis one does. It happens to break through, and in that case the boat sinks. In that case, the lay people will say the cause of the sinking was the one pellet that actually makes a hole.

Q: Are there mechanisms in nature where you have differences like that, where a chemical or drug or radiation or something else might cause a risk each time there is an exposure, but each one is not causal and something finally happens?

A: In risk assessment, if you are talking about dose and response issues in things like radiation, it is a one-hit hypothesis. In other words, one dose could cause — trigger a set of events.

Sometimes we see things in which you get a concentration of chemicals that have to have been built up beyond a threshold, before anything starts to happen. There has to be sort of an accumulation of the chemical.

And you see this oftentimes in fat soluble chemicals that can lay in the body, be there for longer periods of time, and not be immediately excreted.

So, therefore, you can have a longer term of exposure without seeing anything. Then all of a sudden you start seeing toxicity.

Q: So there are different models of how things occur in different situations, comparing one to another?

A: Yes.

Q: Is there any way to tell, on the basis of the data with respect to these drugs, what kind of situation we have here, whether it's a one-hit model or whether it's accumulative?

A: I don't think we have enough data to say that, to specify.

Q: Let me show you what has been marked for identification as Defense Exhibit C and ask you if you can identify that for us?

A: These are short-term latency period studies that were done where they took Alpha and then took three months of Gamma. And it shows once again that the Gamma was at least six times more toxic than the Alpha.

Q: I'll put this up on the board here in just a second. But before I leave Exhibit B, let me ask you —

THE COURT: Mr. Smith, before you do that.
Counsel, could I ask you both to step up for a moment?
(Discussion off the record.)

Q BY MR. SMITH: Doctor, let us look at the relative adverse rates that you distilled from the three clinical reports where you show that the data indicates the Gamma was almost 29 times more risk-producing toxic than the Alpha.

If these drugs cause photoneuritis, absent any knowledge or proof these drugs act in an accumulative way as opposed to a probabilistic way, where each dose creates a risk and then the risk may be gone and not affect the ultimate outcome, would it be fair to say that if somebody took Gamma and Alpha in equal doses, it would be almost 29 times higher risk than if the disease that occurred had come from the Gamma?

A: It's possible, but we don't have enough data to substantiate that. If they were taking them simultaneously, there could be some synergistic effect.

Q: We just don't know at this point?

A: We just don't know.

Q: Let me put up on the board Exhibit C, which you mentioned in your testimony. As you indicated, this has to do with the latency data, that is, how quickly the disease appeared after the various drugs were taken.

We know Mr. Schuman took Alpha for eight months and that he took Gamma for eight months thereafter.

Looking at the data in terms of the comparative risks of Alpha and Gamma, even when much more Alpha drug was taken by the individual, does this give any indication that the Gamma drug was more risk producing?

A: Based on these data, yes.

Q: So if this drug acted in a probabilistic way — and you have testified you don't know — would it be correct to say that it was six times more likely that the Gamma caused the illness than Alpha?

A: I would say yes.

MR. SMITH: At this point I don't have any further questions, Doctor. I will turn the witness over to Mr. Black for cross.

THE COURT: Cross-examination.

CROSS-EXAMINATION BY MR. BLACK

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Q: Dr. Toscano, I understand that much of your work has involved research on the in utero effect of drugs. Is that correct?

A: Yes.

Q: That's not at all an issue in this case, is it?

A: No.

Q: And you have also done research on how drugs or exposures to other substances might interact with other factors in a person's life?

A: Yes.

Q: Now, if you had a situation wherein a drug had an adverse effect on people who consume grapefruit juice and there was no adverse effect on people who did not consume grapefruit juice, you would still say that in the general population the drug was causing an increase in the incidence of the adverse effect. Isn't that right?

A: It depends on how many people and how much you see. Take the example of grapefruit juice. Unfortunately, we know the mechanism of how that works in the sense that there are enzymes in the liver that metabolize drugs, which is a good thing because you don't want to build up too much of a drug condition because you could have a deleterious effect. So if you take a drug, some gets metabolized by this enzyme called cytochrome P450 in the liver.

Q: You need to speak up.

A: Cytochrome P450. And then they get metabolized, and you can excrete them, which brings the level down. So for dosing regimen you try to get some level of balance. Unfortunately grapefruit juice inhibits that enzyme. So you can't metabolize it away. So grapefruit juice would greatly enhance the risk of an adverse event.

Q BY MR. BLACK: That's a very interesting discussion about how the mechanism of grapefruit juice really works. Now I would like to get back to my question.

THE COURT: Nothing personal, counsel, but you introduced it.

MR. BLACK: That's true.

Q: But I don't think the answer was responsive, your Honor. Let me explore it a different way. Let's say that it's jelly beans, and nobody has a suspicion about jelly beans.

You have Drug A. And Drug A is fine in people who don't eat jelly beans, but if you eat jelly beans at the same time, you develop ulcers.

Suppose you were unaware of the need for jelly beans in order to interact with the drug. You saw a population where before there was an incidence rate — let's say, one in 200 of ulcers — and in this drug population, it went to ten percent. It's increased by twentyfold; you saw a twentyfold increase like that. That would be evidence that in that population, without making any distinction about jelly beans, the drug was causing ulcers. Is that right?

A: It depends on the number of people. So if it's a small study, it really is not necessarily relevant.

You take a case of, for example, the avian influenza. In a small population, everybody who had avian influenza died. So it's 100 percent.

But as you start looking at data further, it's not relevant because many people now have been infected and have not died. So as you spread it among the population, different susceptibilities make some people have an adverse effect and others not.

If the study is small, I couldn't say that. If the study is large, then it's another story.

Q: Again, that's a very interesting answer. But you're still not addressing the question.

My question is this. You could have a circumstance where you don't know about the co-factor and you have a population where there's a marked increase in the incidence of some adverse effect or disease. In that circumstance, you would say that, without making the distinction between people who eat jelly beans and don't eat jelly beans, in the overall population the drug has caused an increased incidence of the adverse effect. Correct?

A: I don't know if it caused it. I could say it may be related to it. It could set in motion a number of events that are related to it.

I have difficulty saying cause. Cause and effect are difficult for me.

Q: You could say associated?

A: I could say associated, yes.

Q: Now, I want to get some of your general causation analysis in this case.

In reading your report and in listening to your testimony today, you have indicated that one factor you have considered in reaching your conclusions in this case is there is no defined mechanism through which the polystatol drugs might lead to photoneuritis. Is that correct?

A: Not necessarily. What I concluded from the mechanistic studies was that the one published study was a small study and that, in fact, it goes against what we observed in other kinds of data with those kinds of enzymes.

So, from that I conclude that we need more mechanistic studies to figure it out in a rational way.

Q: To figure out the mechanism in a rational way. Is that correct?

A: Correct.

Q: But you wouldn't need mechanism to reach a conclusion about the causation, would you?

A: Not necessarily.

Q: Well, let's explore that a little bit.

A: Well, sometimes to understand biological feasibility, mechanistic data is very valuable. So animal studies can actually be useful in

understanding human studies, human results, even though we know that mice have tails and that humans don't. But the genomes are not that different, in fact.

There's about an 80 percent concordance with mice genomes and human genomes. So many of the things are very similar, and work in very similar ways so that we can start making judgments and do better experiments to understand how the mechanism would occur.

The mechanistic data are valuable in understanding biological relevance. If we had an epidemiology study that said something, but it can't happen biologically, what would that mean? So that's what I was getting at.

Q: Does cigarette smoke cause lung cancer?

A: I don't know.

Q: You don't know?

A: I don't know. But you ask if things in cigarette smoke cause cancers, yes.

Q: What are the things in cigarette smoke that cause cancer?

A: Things like benzoapyrene, for example, which is a combustion product that gets converted into a cancer-causing agent.

Q: Do we know the mechanism?

A: We do, actually. But many people who smoke don't get lung cancer.

Q: Let me ask the question differently. Was a conclusion about cigarette smoking and lung cancer reached before there was any understanding of the mechanism?

A: No.

Q: It is your testimony, no?

A: No, because the mechanisms of action of those agents were studied long before it was recognized that lung cancer and cigarette smoking were associated.

Q: I think we might hear some different testimony on that point from Dr. Greenland.

THE COURT: That remark by Mr. Black was a volunteered statement and may be stricken.

Q BY MR. BLACK: Does Thalidomide cause birth defects in the children of mothers who take the drug while pregnant?

A: It depends on when they take it and at what stage of the development that they take it.

Q: The answer is, yes, it causes birth defects in the children of mothers who take —

A: It's associated with birth defects. We don't know the cause.

Q: We don't know the mechanism?

A: We don't know the mechanism of how Thalidomide works in any instance, in fact.

Q: Is it your opinion that there's been no finding in the scientific community that Thalidomide causes birth defects in mothers who were taking the drug while pregnant?

A: I can't say that it causes it. Certainly it is associated with that exposure.

Q: I would like to show you Plaintiff's Exhibit 1, which is an article that was published in 1962 in the *Journal of the American Medical Association*. Are you familiar with the *Journal of the American Medical Association*?

A: Yes.

Q: That's a highly regarded peer-review journal?

A: By some, yes.

Q: Would you not be among the some?

A: I am not among the some, to be honest, but that's an opinion.

Q: Okay. Is Johns Hopkins generally considered to be a pretty good medical school?

A: It's an okay place.

Q: So here in 1962 in this perhaps okay journal, we have Dr. Taussig, a professor from perhaps an okay medical school in Baltimore, publishing an article entitled "The Study of German Outbreak of Phocomelia."

What's phocomelia?

A: It's where the limbs look like seal arms instead of regular arms with digits.

Q: So it is a form of birth defect?

A: It is a form of birth defect.

Q: It is the form of birth defect most commonly associated in the children of women who took Thalidomide. Is that correct?

A: Yes.

Q: For those maybe not as old as some of us here and who don't remember the Thalidomide case, I'll show you some pictures.

These are pictures. It's not very clear, but you can see the arms missing in the upper left and the deformity in the foot in the next picture.

I think that's enough to indicate the severity of the birth defects that were associated with Thalidomide.

Is that the kind of birth defect that you understand would have been associated with Thalidomide, Doctor?

A: Yes.

Q: And are you familiar with this article, the article by Dr. Taussig?

A: Yes.

Q: I would like to call your attention to page 1110 of this article, and I will read this and then put it back down so the audience can see it, too.

First of all, let me ask you this question. When was it first recognized Thalidomide might be related to birth defects? Do you recall the year?

A: I think it was 1961 or 1960.

Q: Would November of 1961 sound right to you?

A: That sounds right.

Q: This is what Dr. Taussig wrote: "Thus, between November 20th, 1961, and January of 1982." That's, what, two or three months?

A: 1982?

Q: 1962, two or three months?

A: Yes.

Q: "The circumstantial evidence." The circumstantial evidence was case reports. Correct?

A: Uh-huh.

Q: "The circumstantial evidence rapidly accumulated in different parts of the world, which indicated that Thalidomide played an important role in the production of phocomelia."

Does that sound right to you?

A: That's true.

Q: If you want, you can read it. There it is in the article.

So within three months, based on adverse event reports, there was recognition that there was a relationship between Thalidomide and this particular form of birth defect. Is that correct?

A: That's correct.

Q: And how long after November 20th was it before the drug company removed Thalidomide from the market?

A: You know, I don't know. I know it was never introduced in the U.S. I don't know when it was withdrawn.

Q: Does two weeks sound right to you?

A: That sounds good.

Q: That had the drug company pretty convinced. Right?

A: I would say so.

Q: In doing that, it is also true, isn't it, that Thalidomide was sold in Germany under the name Contergan? Is that correct?

A: Yes.

Q: It was the biggest selling drug in Germany at the time. Is that correct?

A: It was.

Q: So this was a big step for the drug company to remove it from the market?

A: It was, but not all children had this disease.

Q: I understand that. But it's okay to leave the drug on the market because it's only some children?

A: I didn't say that. No, I didn't say that.

Q: Are you familiar with a drug called Cisapride?

A: Yes.

Q: Did Cisapride cause heart arrhythmias in some people who took it?

A: Some people, yes.

Q: And that's generally understood in the scientific community?

A: Yes.

Q: What is the mechanism through which Cisapride causes —

A: I don't know. However —

Q: You don't know, but for today's purposes I will not move to strike. Give us your "however."

A: You don't know how many cases or anything more about the individuals. It's difficult to assess actual causality of these things in all people.

And so the population is again widely distributed. Things are parsed.

Some people are very sensitive while other people are insensitive to some drugs. And we more or less fall in the middle, sensitive or nonsensitive or have some level of sensitivity.

And you can even see this in some of these very toxic agents that people are exposed to. Some people don't show a reaction, but other people show at very small levels of reaction.

So something is different about their physiology that makes them susceptible or more sensitive to these agents.

Q: That's an explanation as to why some people suffer an adverse effect and others don't. Is that right?

A: Yes.

Q: In the population, you would say that the drug is causing, in some cases, the disease?

A: Yes.

Q: Are you familiar with a publication called *Drug Safety*?

A: Yes.

Q: Is that a peer-reviewed journal?

A: Yes.

Q: Is it a well-regarded journal?

A: By some.

Q: By you?

A: By me, no. But that doesn't mean anything.

Q: You rank it right down there with the *Journal of the American Medical Association*?

A: Probably true. Probably even lower than that.

Q: Well, in this inverted world that might not be a bad thing.
I'll strike that comment.

THE COURT: Or I would have.

MR. BLACK: I suspected as much, your Honor.

Q: Before I show you this article from the *Journal of Drug Safety*, are you familiar with a drug company called Eli Lilly?

A: Yes.

Q: Would you expect a scientist who works for Eli Lilly to say that there is a causal relationship between a drug and an adverse event if in fact there were no such causal relationship?

A: I wouldn't expect it if it was an Eli Lilly drug; but if it was a Merck drug, yes.

Q: Let's take a look at somebody who was talking about an Eli Lilly drug.
And the title of this article is "Application of the Bradford Hill Criteria to Assess the Causality of Cisapride-Induced Arrhythmia." Did I read that right?

A: Yes.

Q: And you will see the second author is someone named Simon Walsh. Do you see that?

A: Yes.

Q: And you look under number 2, he works for Eli Lilly & Company in the United Kingdom. Correct?

A: Yes.

Q: I don't want to take our time up getting into all the details of this article, but let me read to you under "Results."

"The most compelling evidence of the association between Cisapride use and QTc," and the QTc is heart arrhythmia. Correct?

A: Yes.

Q: "The most compelling evidence for an association between Cisapride use and QTc interval prolongation/arrhythmia came from case/spontaneous reports and biological plausibility." Is that correct?

A: Yes, that's what it says.

Q: No epidemiology study. Correct?

A: That's right.

Q: And yet there was a conclusion reached about a causal relationship?

A: No, it says association. Association is different from cause. It's very difficult to show cause and effect events in biological systems. But there can be an association that is found.

How strong that association is, that's another story.

Q: Okay. Let's get to the bottom line. I don't want to take up our time today going through all of the factors that they looked at. I want to establish there were no epidemiology studies here. We can agree on that?

A: Yes, we can.

Q: And the author of this article went through some other factors. And if you want to, we can talk about those other factors.

But I want to get to the bottom line here. "Nevertheless, this did not prevent the assessment of causation." Did I read that right?

A: Yes.

Q: But there was here an assessment of causation. Correct?

A: I think causation is misused, oftentimes, even in epidemiology studies. They don't go through the rigorous evidence that Dr. Greenland and others have put forward to show what causality is. They may make associations. And even epidemiology studies are not sacrosanct.

There are a lot of errors that occur that are never mentioned and are taken into account in the conclusions made from the epidemiology studies.

So I wouldn't call epidemiology a physics kind of experiment. Nor would I call what's done in biology with the same certainty that physicists can say about things that occur in their world.

Q: When we're talking about physicists, we're talking largely about mechanism. Right? That's the first argument.

A: Cause and effect.

Q: That was one point that you made. And epidemiology is something different than mechanism. Correct?

A: Yes.

Q: We didn't have either in the case of Cisapride. Correct?

A: Yes.

Q: "Nevertheless, this did not prevent the assessment of causation." Did I read that right?

A: That's what he said, but that doesn't mean it's true.

Q: So you disagree with this drug company scientist, among others. Right?

A: I do.

Q: Do we know the mechanism through which aspirin reduces inflammation?

A: We have some idea.

Q: We have some idea today?

A: Yes.

Q: How long has aspirin been used as a drug?

A: I don't know. It's been used for a long time.

Q: About a century?

A: Probably more. It has never gone through a rigorous study or approval. It's generally accepted as a safe drug.

However, if you were to try to put aspirin on the market today, it would be a different case. They would have to go through drug studies, clinical trials, and so on to try to get approval from the FDA.

And whether they would get approval is another matter. We don't know.

Q: That's very interesting.

Let me repose the question, which was does aspirin reduce inflammation?

A: Yes.

THE COURT: That was actually not the question.

MR. BLACK: It is now, your Honor.

A: It reduces inflammation, yes.

Q: Do we know the mechanism?

A: We have some ideas.

Q: We have some idea, but we don't know the mechanism?

A: We don't know the entire mechanism because one of the things that we find in biology is that more than one thing happens. So you

take a drug. And the body is a system. As I said earlier about how we are all sitting here and signals are going on all the time, they are talking to one another. All this stuff is going on at one time.

So if you tweak the system here, it's like Jell-O. You touch the Jell-O, it starts to wiggle. Over here the Jell-O is also wiggling. So it's not just one thing that's related to how a drug works or how drugs cause toxicity.

Q: Does Jell-O have anything to do with the mechanism by which aspirin reduces inflammation?

A: Yes.

Q: I will not ask you to elaborate on that.

While I'm locating my exhibit here, you suggested that aspirin has been generally accepted as safe because it's been around for 100 years and people have understood for 100 years that it reduces inflammation.

If one were to try and put aspirin through FDA approval now, would it be necessary to explain the mechanism in order to obtain approval?

A: No.

Q: This is another copy of the slide that Mr. Smith showed you.

THE COURT: Do we know its exhibit number?

MR. SMITH: B.

MR. BLACK: Exhibit B. Thank you, Mr. Smith.

Q: What I want to focus on is that you have taken a look at the clinical trial ophthalmologic events for the various polystatol drugs. Correct?

A: Yes.

Q: And there was one such event with AlphaSoleCure. Right?

A: Yes.

Q: Two with BetaSoleCure. Right?

A: Yes.

Q: Ten with GammaSoleCure?

A: Yes.

Q: How many with the placebo?

A: Zero.

Q: So none occurred when people don't take the drug in the clinical trials. And we have 13 with people who were taking one polystatol or another. Have I got that right?

A: Yes.

Q: Let's take a look at Exhibit C again.

And we talked about latency periods. I want to clarify a little bit my understanding of latency.

This slide focuses on the number of doses taken before the onset of the disease. Is that right?

A: Yes.

Q: I understand that use of the word "latency." But there's another use of the term "latency" which would be that you take one dose and maybe the disease doesn't appear for sometime afterwards.

Do you understand that use of the term latency?

A: Yes.

Q: And one example would be with asbestos where somebody could have an exposure 25 or 30 years ago and not develop a disease until today. Is that right?

A: Yes.

Q: So that kind of latency or gap in the appearance of the disease between exposure and appearance of disease, that's another form of latency. Is that right?

A: It is, but in the case of cancer it's a different kind of problem because cancer has different multiple steps, multiple mutations, other things that can be corrected in the cells with DNA repair and other things which could delay the onset of disease.

So typically in this kind of drug effect, you would not see much latency because it's quicker acting and the reduction would be quicker as well.

So I doubt in this case that — because there are no mutations that are involved as far as we know. We don't know the mechanism, because it hadn't shown up. And if you look at the number of doses and the number of cases, the doses with Alpha were many more, and you have about the same number of cases as you do with the Gamma. So I would say the Gamma is more likely than the Alpha to be a problem.

Q: We don't know the mechanism?

A: No, we don't know the mechanism.

Q: I appreciate the discussion of why you have latency with cancer, but this isn't a cancer case.

A: Right, but you brought up cancer.

Q: You can have latency with diseases that aren't cancer. Is that correct?

A: Sometimes you can. If you start activating the immune system, then you have other exposures that come on later, yes. But oftentimes, most times, the onset is early.

However, if you are talking about complex diseases like Type 2 Diabetes or heart diseases, there is a long latency between what people would ascribe to the event that led to that and the time you see the onset of the disease.

Q: I think I understand that, but let me move on. We don't know the mechanism here?

A: Right.

Q: You can have latency with diseases other than cancer?

A: Right.

Q: And it has been reported that that there are several instances where people develop photoneuritis three or four months after their last dose of a polystatol. Is that correct?

A: Yes.

Q: So if a person were to have taken AlphaSoleCure, took no polystatol for three months, and then developed photoneuritis, there's a real possibility that the AlphaSoleCure could have caused it. Correct?

A: I believe that wasn't the case in this instance.

Q: I understand you believe it wasn't the case here. However, please answer the question.

A: I don't like the question because —

Q: I could understand why you don't like the question. Please answer.

A: Because it's not relevant to this case. We don't know. The answer is we don't know because we don't have data to look at.

Q: If a person took eight doses of AlphaSoleCure, then took nothing else for three months, and then developed photoneuritis, it could have been the AlphaSoleCure that did it. Right?

A: We don't know.

Q: You don't know. It's possible it could have. Right?

A: Everything is possible. We don't know. You don't have data to substantiate such conclusions.

Q: We understand there could be a latency period. Correct?

A: In some cases that happens, but it hasn't been shown here.

Q: We understand that with polystatol, there could be a latency period. Correct?

A: We haven't shown that.

Q: There is evidence that there is a latency period in some of the cases of people who developed photoneuritis after taking the polystatol?

A: No, they stopped taking the drug, and then they got the polyneuritis.

Q: Photoneuritis.

A: That doesn't mean that that's the cause. It's very difficult to assess whether the drug, after stopping, was the cause without more information.

Q: You and Mr. Smith went through an interesting example about firing pellets at the boat and whether it sunk the boat — whether it put a hole in the bottom or whether it piled up and weighted the boat down.

If you had a situation where the pellet hits the boat and it's a slow leak, the boat doesn't sink right away, we've got a latent sinking. Do you understand my use of the analogy?

A: I do understand it.

Q: Okay. The boat's going to sink; it's just taking it a while to sink. Whatever happens afterwards other than patching up the leak or pulling the boat into a dock, the boat's going to sink. Right?

A: Probably.

Q: So if the AlphaSoleCure after eight doses had put Mr. Schuman on the track to give him photoneuritis, he was going to get it no matter what happened afterwards. Correct?

A: It's possible, but we can't conclude that from the data we have.

Q: But conceptually in terms of your example with the boat —

A: All things are possible.

Q: Now, we've mentioned epidemiology a number of times and the supposed need for epidemiology. There's no checklist set of criteria for determining whether an association is causal or not, is there?

A: No.

Q: And in fact, we often hear of the Bradford Hill criteria. The drug company scientist used the term Bradford Hill criteria in this article. Right?

A: He did.

Q: But the considerations that Professor Hill outlined, they weren't, strictly speaking, criteria. They were factors to be considered in assessing causation. Correct?

A: Yes.

Q: Just to be clear for the Court — for our audience. With the Court's indulgence, I have an exhibit that I think will help on this.

THE COURT: All right. Why don't you take one second and explain Bradford Hill and what we're talking about here.

MR. BLACK: Your Honor, that's what I was —

THE COURT: Excellent idea.

Q MR. BLACK: Are you familiar with the publication where Professor Hill outlined these criteria?

A: I am, but that wasn't a peer-reviewed publication. That was from a speech that he gave.

Q: Let's take a look and see exactly what it was. First of all, what was the date?

A: Looks like January 1965.

Q: And it says, "President's Address." Is that correct?

A: So what?

Q: And this was an address made to whom?

A: To a Royal Society of something, but I don't remember what.

Q: Royal Society of Medicine.

A: So what?

Q: It was published in the proceedings of the Royal Society of Medicine. Correct?

A: Yes.

Q: And it was Sir Austin Bradford Hill who was giving this address. Correct?

A: That's correct.

Q: At that time, Bradford Hill had been recognized for his contributions to public health by being knighted by the Queen. Correct?

A: Yeah, so?

Q: He was a pretty well-recognized public health scientist. Would that be fair to say?

A: Yes.

Q: And he was recognized well enough that he had been invited —

A: A medical scientist, not a public health scientist. There's a difference.

Q: All right.

A: A dramatic difference in the approaches to the way things go.

Q: I understand the distinction. But he was a pretty well-recognized medical scientist?

A: He was a knight.

Q: And he was recognized well enough that he was invited to give the President's address at the annual meeting of the Royal Society of Medicine. Correct?

A: Yes, that's right.

Q: But we are not supposed to consider this article because it wasn't peer reviewed?

A: It was a speech. Talk is cheap in the sense that you can say almost anything you want to in a talk, and you can't be held liable for it because there was no peer review. No one says, "What data do you have to suggest this to be true." There is no check.

So the check and balance is important.

But it was from a speech he gave, and then it became somehow used as a set of checks, which I think is wrong. But they were checks to get to the delivery of the material.

Q: It would be wrong to use it as a checklist. Correct?

A: I would think so.

Q: Let's take a look. First of all, for the record, let's take a look at what the Bradford Hill considerations are and see what Professor Hill himself said during his speech because I think on this, we may all be in agreement.

These are the Bradford Hill considerations. It comes from the publication "The Environment and Disease: Association or Causation?" And that's the citation, 58th Proceedings of the Royal Society of Medicine in 1965.

I quote at the top there: "If there is an association between an exposure and a disease or health condition," and I'm quoting Professor Hill, "what aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation." Did I read that correct?

A: Yes.

Q: So he's not saying these are criteria, he's saying these are things to consider. Correct?

A: Yes.

Q: And the nine are all on the screen at once. Strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Did I read that right?

A: Yes.

Q: And I will not take the Court's time today to explore what each of those are, but that is an accurate list of the nine considerations that Professor Hill enumerated in his speech to the Royal Society of Medicine?

A: Yes.

Q: His un-peer-reviewed and unreliable speech?

A: Yes.

Q: Let's see what he says at the end. "Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe, and this has been suggested, is that we can usefully lay down some hard and fast rules of evidence that must be obeyed before we accept cause and effect." Did I read that right?

A: Yes.

Q: And with that view expressed by Professor Hill, you are in fact in agreement. Did I have that right?

A: Yes.

MR. BLACK: No further questions.

THE COURT: Redirect.

MR. SMITH: Just a couple of questions, your Honor.

—o0o—

REDIRECT EXAMINATION BY MR. SMITH

—o0o—

Q: Dr. Toscano, just to go back for a second to the Bradford Hill slide that Mr. Black put on the board.

In this particular case with respect to the polystatols, do we have a demonstrated association between taking of the drug and —

A: We don't in this case. So that's an issue, I think.

Q: And let me just ask you because I think it may come up in Dr. Greenland's testimony as well. You discussed and answered some questions with respect to epidemiology and how it can be used to reveal whether or not apparent associations are real. In the epidemiological and statistical world, is there the concept of a nonsense correlation?

A: No, I can't speak to that. I really don't know.

Q: That would be Dr. Greenland later.

A: But I think if you read Dr. Greenland's papers, they rigorously look at what are the criteria and look at errors that could have come in. There's a lot of bad epidemiology out there. And what has to be done is that it has to take on a sense of rigor, statistical rigor, identifying the different kinds of errors that could have crept in before you can make a certainty statement that this X causes Y. I think it's very difficult to do that even in an epidemiology sense.

MR. SMITH: I have no further questions. Thank you.

MR. BLACK: Your Honor, if I might, there's one additional question in light of redirect.

THE COURT: Go for it. Recross.

MR. BLACK: Recross.

—o0o—

RECROSS EXAMINATION BY MR. BLACK

—o0o—

Q: Dr. Toscano, I understood you to say there is no evidence of an association in this case, in the case of polystatols and photoneuritis. Did I understand that correctly?

A: Yes, it didn't meet any of the criteria. None of them has been tested. In fact, if you want to invoke the Bradford Hill concepts, we have to do more testing to find out.

Q: First of all, they are not criteria, they are considerations?

A: Considerations, yes.

Q: We agreed on that?

A: We did. We do.

Q: The nine considerations were factors or things to consider when deciding whether an association in fact leads to causation. Right?

A: Yes.

Q: So you start with an association?

A: Yes.

Q: The question you have raised is whether there is an association at all in the current case?

A: Yes.

Q: Polystatol case?

A: There may be, but we don't have data to suggest that there is.

Q: An association can be established without adverse event reports and without an epidemiological study. Is that right?

A: In some cases. I'm not going to yield on the idea that it would generally be applicable to the population. So, therefore, I think in case reports, you have to know something more about what the person was doing.

For example, was he taking, eating, grapefruit as you pointed out or other things. We don't know those things. We have to look further and have more data to do that.

Q: Thank you for the additional explanation.
But you could establish an association without an epidemiology study. Right?

A: Right, but they haven't in this case.

Q: You could establish an association without an adverse report. Correct?

A: Some people could, but they haven't in this case.

Q: As a methodological matter, let's take a look again at the article from Perrio, et al., and Dr. Voss who was with the drug company. Right?

A: Yes.

Q: And they said, "The most compelling evidence for an association between Cisapride use and arrhythmia came from case/spontaneous reports and biological plausibility." Did I read that right?

A: Yes.

MR. BLACK: No further questions.

THE COURT: Re-redirect?

MR. SMITH: No questions, your Honor.

THE COURT: Let me ask a couple of questions if I can. How do you do a controlled study test or controlled study where the potential malady is very serious? As I understand it, photoneuritis is an irreversible, essentially blinding process. Is that accurate?

THE WITNESS: Yes.

THE COURT: How would you do a controlled study where the alternative to the null consideration is blindness?

THE WITNESS: I think that would be unethical to try to do in that sense in humans. But they did do clinical trials, and these things didn't pop up except in one instance, I think.

So they did do a clinical trial to see whether this was an efficacious drug. And the other result came later. Particularly in this case, it was after he had stopped taking the drug.

So if you are going to induce blindness in people in a study, I think it is unethical, and you should not do that.

But perhaps we can get information from animal studies.

THE COURT: But would you have to create a mouse model or some alternative?

THE WITNESS: Yes, and I think in this disease there is a model for that.

THE COURT: Which is?

THE WITNESS: A mouse model.

THE COURT: Do we know that?

THE WITNESS: I read that somewhere. I don't know.

THE COURT: And I'm also interested in what appeared to be a challenge re-challenge in the data. Can you focus on that, and tell me what, if anything, that information meant to you?

THE WITNESS: The data that were shown by Mr. Smith? The drug control study that we looked at?

THE COURT: Yes.

THE WITNESS: It meant to me the Gamma was probably much more toxic than the Alpha.

THE COURT: That would seem to be perhaps not scientifically supported by the large multiples on the ends.

THE WITNESS: Right. But also if you took the larger — they took fewer doses, they would have the same number of events.

I think there were 300,000 doses of the Gamma, and they had 30 events. And there were 17 million of the Alpha, and they had 27

events. So it was almost the same number of events, but they had five times the number of doses. So it would seem to me that the toxicity of the Gamma would be more than that of the Alpha.

THE COURT: Doctor, I think you said in your research you have a hard time with the concept of causation.

THE WITNESS: Yes.

THE COURT: Have you found a potential disease-causing agent that causes some illness?

THE WITNESS: Have I?

THE COURT: Yes, sir.

THE WITNESS: No.

THE COURT: Okay. Thank you.
Counsel, you may reexamine.

MR. BLACK: Nothing further, your Honor.

MR. SMITH: Nothing further.

THE COURT: Thank you. You may step down.
All right.

MR. BLACK: Your Honor, recognizing the time and the schedule we have set here, perhaps the Court would like us to put Dr. Greenland on for at least qualification and begin his examination before lunch and then take a break?

THE COURT: That sounds fine. We'll call the doctor and then take a break for lunch.
Sir, would you be good enough to take the stand.

—o0o—

SANDER GREENLAND, Ph.D.,

—o0o—

An expert witness herein, called as a witness by the plaintiff who, being first duly sworn by me to tell the truth, the whole truth, and nothing but the truth, was examined and testified as follows:

—o0o—

THE COURT: Sir, would you please state your name and spell your last name.

THE WITNESS: Sander Greenland, G-r-e-e-n-l-a-n-d.

THE COURT: Counsel, you may examine.

MR. BLACK: Thank you, your Honor.

—o0o—

DIRECT EXAMINATION BY MR. BLACK

—o0o—

Q: Dr. Greenland, what is your professional position?

A: I'm Professor of Epidemiology and Professor of Statistics at UCLA.

Q: And now I will put on the screen at least the first page of your curriculum vitae. Does that look like a copy of your curriculum vitae?

A: Yes.

Q: About how many pages long is that?

A: Seventy or something like that.

Q: Let me ask you some questions about it, which I think will clarify your qualifications here. You mentioned teaching. Can you tell us a little bit about the kinds of courses that you teach at UCLA?

A: I teach courses in epidemiologic methodology, study of methods, and epidemiologic statistics.

Q: And are the courses that you teach listed in your curriculum vitae?

A: Yes. I also teach a course joint with the Statistics Department. It's called Logic Causation and Probability.

Q: Is that also listed in your C.V.?

A: It should be.

Q: Have you also listed courses that you have taught in the past on your C.V.?

A: Yes.

Q: So that constitutes a good record of your teaching experience. Would that be correct?

A: I hope so.

Q: Do you also do research?

A: Yes.

Q: Can you tell us about the kind of research on which you focus?

A: Well, the basic division is between actual applied epidemiologic studies, which is about half the articles there, and then the other half, including methodologic research, statistical research, research on methods.

Q: Can you explain to the Court a little bit about the distinction between applied studies and research on methods?

A: Well, applied studies is going out and studying things like the effect of, for example, medical implant devices on health outcomes. So there are actual studies of exposures and diseases. And then the others, methodologic studies, are studying methods instead, for example, studying the use of power for analysis data versus other methods.

Q: So would it be fair to say that the applied studies are actually doing the work and the methodologic studies are research on how the work should be done? Would that be a fair way of describing it?

A: That sounds good.

Q: And you have done both of those. Is that true?

A: That's correct.

Q: And that work is described in your C.V. Is that correct?

A: Yes. The methodologic work is further subdivided into what sometimes are called theory and methods. There's the theory of methods and the actual studies of the methods.

Q: And you have done both the theoretical and the application of the theories or the research?

A: Yes.

Q: How many peer-reviewed publications have you authored or co-authored?

A: About 350, plus a whole bunch of book chapters.

Q: We will move to them in a minute. All these publications are listed in your C.V.?

A: I hope so.

Q: Any reason to doubt that they are?

A: Well, it gets to the point where you go through it, then you realize that something was missing or something needs updating or page numbers were wrong. Just typos.

Q: But as far as you know, this copy of your C.V. is dated September 15, 2011. Is that the most recent version of your C.V.?

A: Not now.

MR. BLACK: Your Honor, it is the version that I have. And with the Court's permission, we'll provide both to the Court and counsel a more updated version of the C.V.

THE COURT: Hearing no objection, it's admitted.

Q BY MR. BLACK: How many books have you written?

A: Well, I co-authored a textbook, *Modern Epidemiology*, in a couple of editions. And I have also served as an editor, which involved some writing as well, for a book called *Evolution of Epidemiologic Ideas*. And for the *Dictionary of Epidemiology* published under the auspices of the International Epidemiological Association.

Q: Now, *Modern Epidemiology*, should I call it a textbook?

A: Yes.

Q: Is that widely used in a number of schools?

A: Yes.

Q: What kind of schools? Do medical schools use that textbook?

A: I don't really know or have a survey. I know it's used in a lot of epidemiology programs in schools of public health. Sometimes those programs exist in medical schools, and sometimes they are not.

Q: Do you have any idea in terms of book sales where it ranks among epidemiology textbooks?

A: Very high at that level because it's an advanced textbook. There aren't many of them. But it sold tens of thousands of copies which is quite a lot for textbooks at that level. It far exceeded our expectations when we wrote it.

Q: Who did you write it with?

A: Ken Rothman was the original author.

Q: When you refer to "our," you are talking about your expectations and Dr. Rothman's expectations?

A: Yes.

Q: Where is Dr. Rothman located?

A: Boston University.

Q: And when was the first edition of *Modern Epidemiology* published?

A: He published that in 1986, and I joined in the second edition in 1998.

Q: So it's been around for about 14 years?

A: Yes, there's a third edition in 2008, with an additional co-author.

Q: I think you mentioned this already, but have you also published chapters in books where you are not the author or co-author?

A: I'm not the editor of the book, but I'm an author of one of the chapters.

Q: Let me rephrase the question because that was a bad question. Have you authored chapters in books where you are not listed as the editor and you are not listed on the front as one of the primary editors?

A: Yes.

Q: About how many such chapters have you written?

A: About 20, I think.

Q: The books that you mentioned are included in your C.V., I take it. Is that right?

A: Yes.

Q: And these chapters would also be listed in your C.V.?

A: Yes.

Q: Have you been elected to fellowship at any professional societies?

A: Yes.

Q: What are the societies?

A: The Royal Statistical Society and the American Statistical Association.

Q: Let me be clear on this. When I say "elected," that's not something that you just sign up and join. You have to be elected to the society. Is that correct?

A: Right. That's right. You have to be nominated and go through whatever process they have.

I wouldn't make a big deal out of those because there's a lot of fellows. And the conditions for the Royal Statistical Society are not tremendously strong. And then the ASA is not even that tremendously strong. There's hundreds and hundreds of fellows in the society.

THE COURT: And you've got only two.

THE WITNESS: Yes.

Q BY MR. BLACK: How many other societies would be available to a statistician?

A: Well, with the title fellow, I don't know. I imagine there might be in other countries. For example, in Russia they might have something royal — clearly, in the United Kingdom. So other countries would have theirs, but I'm not in those countries.

Q: Is it fair to say that you have been elected as a fellow in the two societies or associations, in the two leading societies in the English speaking world?

A: Yes.

Q: Are you a member of other professional societies or associations where election to membership is not required?

A: Yes.

Q: Could you share with the Court —

A: Actually, I'm not up to date on what memberships I remembered to pay my dues. I do know that I did pay my dues for the Society of Epidemiologic Research, which is the major North American society. But the rest I'm not — I can't —

Q: There are others that you belong to, but you are not sure if you kept the membership current?

A: Yes.

Q: The others, if you have let it lapse, it would simply be a matter of sending in a check and rejoining?

A: Right. They are open societies.

Q: Have you served as a peer reviewer for any journals?

A: Yes.

Q: Could you share with the Court some of the journals for which you have done peer review work?

A: There's dozens and dozens of them. But the major ones in the fields I am in are *American Journal of Epidemiology*, *International Journal of Epidemiology*, *The Annals of Epidemiology*, *Biometrics*, *Journal of the American Statistical Association*, *American Statistician*, and then *Journal of the American Medical Association*, *New England Journal of Medicine*. And there's lots and lots. I couldn't possibly remember all of them.

Q: About how much of your time is taken up doing peer review work?

A: Like with most of our colleagues, more than we wish for. But it's a payback for them having published your work. You can bet that if they accept your paper, you're going to get papers from them to review.

Q: This is not necessarily relevant, but my father was a biochemist by profession, and he was a reviewer for a number of journals. And I can remember many weekends lost while he was doing his peer review work instead of doing other things, like going to ball games.

Would you say that is the level of work you do on peer review? Do you put so much work on peer review where it takes up weekends from time to time?

A: Cumulatively. I multi-task.

Q: We are digressing here. I apologize, your Honor.

THE COURT: We are getting, as we say, a little afield.

Q BY MR. BLACK: What experience have you had in evaluating safety of pharmaceutical products?

A: I have been involved in a fair number of studies involving medical products, both devices and pharmaceuticals. And I have also sat on FDA panels for review, applications for approval, approval for use, and other advisory things. I've been in mock approval panels for drug companies and also consulted with drug companies on some of the issues, such as safety.

Q: On about how many FDA panels have you sat? How many have you participated in?

A: I don't remember during the course of my career. But not that many. I would bet less than ten, but I don't have a good memory for that.

Q: Have you had experience in determining the probability that a medical treatment or drug causes an adverse effect?

A: Yes.

Q: Could you describe that experience to the Court?

A: Well, in the course of doing all the work that I just mentioned, especially the studies of safety of devices and drugs, and the methodologic articles on that, I look at probable causation. That topic in particular occupied a lot of articles I have written. And some of those articles are co-authored. Some of those articles appeared in epidemiological journals, some in statistical journals, and some in law journals, summarizing all that other academic work for a wider audience, I hope.

Q: So to be clear, you have published articles on the question of how to determine if a causal relationship exists between exposure and health effect?

A: Oh, yes, quite a few.

Q: Were those publications peer reviewed?

A: Yes.

Q: Would it be fair to say that you consider yourself to be an expert on the issue of medical causation?

A: Yes, with a caveat depending on how you define that term. I'm a little uncomfortable because I don't draw a sharp distinction as some might between medical and epidemiological. They are so tightly intertwined.

Sometimes epidemiologic evidence is used in medical, and sometimes medical leads back to epidemiological. You try to separate your heart from your coronary artery. Very delicate.

Q: We'll get to this in more detail when we get past the qualifications, perhaps after lunch.

Could you explain to the Court how you conceptualize causation?

A: Well, it would take a little bit of time.

Q: Should we perhaps defer that question until after lunch, if it's going to take a while?

A: Do you want to go until the noon hour?

Q: Go ahead.

A: There are different ways of conceptualizing it.

THE COURT: That's a big question. It isn't real long, but it's a big question.

THE WITNESS: I'll try and improvise the shortest answer that I could.

First of all, there's no single way of doing that. It's one of these topics that has been studied and debated at length by scholars and many other minds better than mine since — for thousands of years.

And today there are whole books on this. There is a book called *Causality* and other similar books on the topic.

Currently in the fields I work in, especially in statistics and related areas of artificial intelligence research and epidemiology and social science, there are several different causality models and conceptualizations that are closely related.

The one that would be perhaps more familiar to a legal audience is basically the statistical version of the but-for causation idea. That is sometimes called the counterfactual causal model, the potential outcomes model, or the Rubin causal model, which is something we always cringe at because he didn't invent the model. But there's a law in statistics called Stigler's Law of Eponymy, which says that if a method is named after someone, it will be named after the person who didn't invent it.

It was really first formally proposed in the early 1920s by a statistician and named long before Rubin or I was even born.

And it could be traced earlier in concept.

And that one is just but-for, basically. It says something is a cause if you got this disease but you wouldn't have gotten it had you not gotten this exposure.

Like you wouldn't have died at that moment if you hadn't gotten that bullet through the heart from the gun pulled by the defendant, for example. But —

THE COURT: The husband said his wife's lover died of natural causes when the knife pierced his pericardial sac.

THE WITNESS: So basically the model focuses on counterfactual potential. I call it potential outcomes model. We primarily call it that in the book, referencing the other uses.

That one is just the formal, logical version of the but-for idea. Every person has associated with them an outcome when they were exposed and an outcome when they weren't exposed. And then what happens may depend on whether they were exposed if those two outcomes are different. So we say something is a cause if indeed their outcomes are different under those two scenarios or would have been different if we are talking historically.

That's my impression. The largest one in the literature is that basic analog of the but-for idea. But there are other conceptualizations, which have strong logical links to that but go into more detail like the sufficient cause model, which is often in my field attributed to Rothman, my co-author, senior author, but actually can be traced before him.

This sufficient cause model creates more detail. To have the situation, where you have this but-for situation you have to have components of the causation coming together. It's not just one exposure, but different co-factors enter it.

And then there are other models, which are instead in the opposite direction, more broad and less fine in the detail of causation, but involve webs of causation like the graphical causal models or causal diagrams. We also have a chapter about that in the book, *Modern Epidemiology*.

And that's very popular, especially in artificial intelligence research. Computer scientists and engineers like them because they are mapping out whole complex systems. It's also been used in social sciences a lot. It's entering epidemiology through our book.

Q BY MR. BLACK: What model of causation have you used in reaching your conclusions in this case?

A: In this case, I would say it's focused more on the traditional epidemiologic sufficient cause model but more basically the but-for cause model.

Q: Would it be fair to say you consider yourself an expert — strike that. Have you ever testified in court before?

A: Yes.

Q: About how many times?

A: In court, in actual as opposed to deposition, going back twenty-five, thirty years, I think it's less than a half dozen instances of actual testimony at trial, including hearings. But there are several times recently — sometimes I don't remember exactly if it was a hearing or trial by judge, but I've done some. But a lot of depositions.

Q: Has your testimony ever been excluded by any court?

A: I don't think so, but I don't know the technicalities because there was one case where the judge basically said, "I can't testify to that" because I'm not a physician. I said, "I'm not a physician, and I won't testify about certain things because I'm not a physician." And the judge turns to the plaintiff's lawyer and says, "You better get yourself a physician."

Q: So when you yourself said you couldn't testify about something, the court wouldn't let you testify about it?

A: And that was the end of my involvement. So I think that was the case.

MR. BLACK: Your Honor, no further questions at this time.

THE COURT: This looks like a good time to take a break. We will be in recess for lunch to return at one o'clock. We are in recess.

(Lunch break taken from 11:50 to 1:02.)

—o0o—

AFTERNOON SESSION

—o0o—

THE CLERK: We are back in session.
Good afternoon, counsel. Are you ready to proceed?

MR. BLACK: Yes, we are, your Honor.

THE COURT: Dr. Greenland, would you be good enough to be seated, step over to the witness stand?
I think we discovered the fact that he had previously testified on a couple of occasions and seemed to be well familiar with depositions.

MR. BLACK: Are we all set?

MR. SMITH: Are you going to put a disclaimer in?

THE COURT: You were previously disclaimed.

Q BY MR. BLACK: You were previously disclaimed, and I will disclaim again for your benefit, as you weren't here the first time.
As we turn to get into some of the general causation opinions, but certainly as to specific causation, we are getting into an area where Professor Greenland might not give an opinion and, in some cases, probably would not agree with the testimony.
I described to you all the problems. *Daubert* is intended to weed out bad experts. And we didn't get bad experts today. So we had to have

them behave a little bit differently. Do you want to add anything more, by way of disclaimer?

THE WITNESS: Well, that I didn't write all that testimony. You probably will be able to tell it apart.

THE COURT: We'll proceed.

MR. BLACK: Returning to our case here, Dr. Greenland. In this case, Doctor, have you reached any conclusions about whether polystatol drugs cause photoneuritis?

A: Yes, it appears that it can.

Q: With regard to Mr. Schuman, you understand that he took two different polystatol drugs. Is that your understanding?

A: That's my understanding.

Q: He took the AlphaSoleCure drug for about eight months. Is that your understanding?

A: Yes.

Q: And the GammaSoleCure drug subsequently for about three months. Is that right?

A: Yes.

Q: That's your understanding again?

A: That's my understanding.

Q: And is it your understanding that Mr. Schuman developed photoneuritis a week after his third dose of GammaSoleCure?

A: Yes.

Q: Have you reached a conclusion about what contributed to his photoneuritis?

A: Yes.

Q: Could you tell the Court what that conclusion is?

A: I think it's more probable than not that both contributed.

Q: So to be clear, the AlphaSoleCure was more probably than not a contributing factor in Mr. Schuman's loss of vision. Is that right?

A: In my estimation, yes.

Q: And what about GammaSoleCure?

A: And again, my estimation, yes.

Q: We'll go back to that point in more detail later on.

Briefly, can you tell the Court how it is possible that two things could be contributing factors to a disease?

A: Well, I like the mechanical analogy that was given by defense in shooting at the boat, shooting pellets into the boat, and shooting pellets onto the boat. In the case where the boat sinks because it's eventually weighted down, clearly even something that's contributing less than the pellets is still something that pushes it over the edge in the sense that, but-for that action, the boat wouldn't have sunk. It wouldn't have reached the critical point or weight where it sank.

And in the other case where it's more random, probabilistic, eventually something penetrates the hull, it develops a slow leak down and eventually goes down. But you don't know which pellet it is. Then you can say only then that this factor contributed to the probability.

You don't know which one of the pellets. Let's say there were two people shooting at the boat. You don't know whose pellet it was, but you can't tell them apart forensically or they are no longer retrievable. You can't tell which one produced the hole that eventually sank the boat.

So you have to say, in probabilistic terms, they were both contributing to the probability that the boat sank, and that event did come about. One did penetrate, but you don't know which.

Q: Let's go back then to your general opinion about polystatols and photoneuritis.

Moving away from the substantial contributing factor discussion about Mr. Schuman. Going back to the general opinion.

In the report you submitted in this case you have written that "Science, in general, and epidemiology, in particular, can never establish a causal relationship with absolute certainty."

Could you explain to the Court what you meant by that statement?

A: Well, I meant that in scientific terms you don't have to, for one thing. General causal laws only have varying degrees of certainty depending on the evaluator. And that includes the evaluator's knowledge and understanding of the evidence and also the vested interest in the evaluation.

Moreover, in any scientific evaluation, there's room for doubt, but that may be so tiny as to be negligible for most evaluators or an entire community, as in the relation of tobacco to lung cancer. By 1964, there was no doubt left among people who had no connection to the tobacco industry, whatever their interest was, that there was this causal link to the use of tobacco.

Or on the other hand, there may have remained large enough doubt for serious dissent to occur in the community. That's occurring today regarding the role of vitamin supplements and disease controversy. There is a lot of controversy now because of the conflicting results and the negative results in trials using synthetic vitamins.

Q: I want to clear up one point because it relates to some of the testimony we heard earlier from Dr. Toscano. When was it clear to the scientific community that tobacco causes lung cancer, tobacco smoke causes lung cancer?

A: Well, it's one of those things that happened gradually. But the U.S. Surgeon General's 1964 report was a landmark point. At that point, the evidence was so strong and so many scientists were coming forward saying this, "Really, you need to do something, this is probably causal," that the Surgeon General did issue this. It led to the warning labels saying we know enough now to take action.

But in first science, pure science, you never reach a point where you are claiming you know causation. You take a theory, and it could remain called a theory and treated as a theoretical object academically indefinitely.

Q: Let me ask you a follow-up question on that because I believe this is where you were going. Is there any sort of checklist set of rules that you follow to establish causation?

A: No.

Q: If there is no set of rules for establishing causation, how is it that you ever reach a conclusion that there is a causal relationship?

A: Well, again, it depends on what you call reaching a conclusion. There can be such a high degree of certainty that you would say action is warranted.

And that would have to depend, too, on the costs of no action versus the cost of taking whatever action is being proposed. The cigarette and lung cancer example was fought very bitterly not only by tobacco companies, but at least by certain scientists who weren't convinced.

You would have to say what's the cost of taking no action at all. And if it's causing lung cancer, the answer is you would continue to have these lung cancers versus the cost of putting a warning label on or versus the cost of trying to ban tobacco. It's an enormous cost now, as we know from drug wars trying to ban a substance.

So there are all these levels of action that could be envisioned and the cost. And the cost would have to be considered if there was no effect. Everybody was wrong, the effect was wrong, or the effect was smaller than indicated by the epidemiology data. Or the effect could be even higher than what was indicated, which is also possible.

Q: Well, I think in explaining how science goes about reaching conclusions, you could talk about quantum theory — whether that's established to a certainty or whether it's accepted. Could you expand on that for the Court?

A: In an ideal science, you never have to reach a conclusion. People do, but you don't have to.

In fact, look at physics. That's ideal for a precise situation. Quantum theory was to be, I understand, the most precise physical theory ever in terms of its potential verification —

UNIDENTIFIED SPEAKER: [Unintelligible]

THE WITNESS: Well, tell me. I would love to be corrected.

UNIDENTIFIED SPEAKER: It's based on things being imprecise.

THE WITNESS: Well, no. That's a misunderstanding. It makes very, very precise predictions about probability, or frequencies of events.

Those are verified down to 20-digit accuracy, and its predictions are borne out.

And still it's called quantum "theory." And still people search for a deeper, more extensive explanation of what's going on.

So the point is that we never have to reach an absolute conclusion. Although there is clearly data for the general theory of relativity, Darwin's Theory of Natural Selection, and many celebrated theories, you still call it a "theory."

Obviously scientists studying them will become more and more convinced that they apply at least in the domains where they are supposed to apply. And after a certain degree of testing has been passed, engineers, physicians, and other people will use these in practice. Then they will say the theory is correct. Then we say that everybody has drawn an inference or a conclusion about it.

But you get into very severe problems when anyone embraces 100 percent certainty because, in that case, they are taking the theory as some kind of absolute truth and faith. The problem is that they are precluding the possibility that the theory breaks down in realms beyond ordinary direct experience, as happened with Newton's laws, eventually. Or the theory might be basically wrong, as appears to be the case with the theory that synthetic vitamin supplements could have health benefits.

THE COURT: We're getting expansive in response to your question. Perhaps we can focus this a little more.

THE WITNESS: Let me wrap that up by saying —

THE COURT: Professor, he will ask you a question.

MR. BLACK: Let me try and refocus, as your Honor was just saying, with a follow-up question.

Q: With regard to epidemiology, does epidemiology ever reach conclusions with 100 percent certainty?

A: I would say no. I don't, although it may get very high.

Q: As I understand epidemiology, one of the things that epidemiologists do is to calculate something called the statistical association between a disease and a suspected cause. Is that right?

A: Yes.

Q: Can you tell the Court how that works? If you want to step to the board to illustrate, with the Court's permission, maybe that will be helpful.

THE COURT: That's fine.

THE WITNESS: All right. So here's a basic starting point.

This is the beginning and can capture fundamentals very well.

This is a two by two table. And this is in terms of quantifying relations in epidemiology. This is a paradigmatic basis. First couple weeks epidemiology. Probably first week epidemiology.

A: So we just fill this out with the numbers. How many of the exposed out of the total got the disease and how many not exposed of the total got the disease. And, in most controversial situations, there is this relation. This may not be a very large difference between these two.

Sometimes, though, we can have an outbreak investigation. This may be a huge relation, where there is nobody here in this box, the box for people who have not been exposed.

Let's take the extreme case where there's nobody here. Zero. But there's people here, here and here. And it's my understanding that this case, that's what we're in.

This is so incredibly rare that the people here never even got the disease, and over here in this box they are getting it. So, in lay terms, it's very suggestive of something causal, although it has to be examined more closely and ultimately.

But still, this is what Bradford Hill was talking about in this number one consideration, the strength of the association. Well, you can't get stronger than to find that you never see this here in this box, but you do see it there. Only the exposed people get this condition.

The strongest, of course, the absolute strongest, is where you have complete causation. That would be the equivalent of getting hit in the head with a cannon shell or something. Nobody survives that. But in the less extreme cases with drugs or devices, you still can have this happen.

If the exposure really was causal, this represented causal relation. And the exposure was responsible for this. Then, we would say that would be a necessary cause, exposure being a necessary cause.

Q BY MR. BLACK: When you quantify association, does that require that you have at least some cases in the disease not exposed quadrant?

A: No.

Q: When you have the disease not exposed box as zero, do you calculate the association the same way you would when there are numbers other than zero in all four quadrants?

A: You can. The two common ways of comparing these are to take their difference or to take the ratio here.

I actually don't have the numbers with me. But if I put in the numbers from this case and took the ratio, I would come up with an infinite number because I'm dividing by zero.

If I take their difference, I would get whatever number is here, whatever percentage.

Q: Focusing on the ratio as the measure of association, you wind up with an infinity when you have zero in the not exposed box. Is that right?

A: Yes.

Q: So in that circumstance, you can't calculate the ratio as you would in the situation where you had positive numbers in every one of the quadrants?

A: It depends. If your background is in math like me, then you are not bothered by putting in infinity.

Q: Do you need to have the quantified association in order to reach a conclusion about causation?

A: Not always fully quantified in some precise fashion. Just to some degree that you would say there is an association and it's so strong that it's hard to explain away.

Q: What about the circumstances that we have here. There was a rare disease so that you essentially have zero in the not exposed box, but you have instances of the disease occurring in an exposed population. Under those circumstances, do you have to have a precisely quantified calculation of the association in order to reach a conclusion about the causation?

A: I would say no. There's always some imprecision that's accounted for. There's a minimum amount that you are supposed to account for, as a statistician anyway. It's called allowing for random error.

Now in a situation like this, it's considered the minimum background uncertainty that you would have. Even if this was a perfect randomized trial — which it isn't — you would still have this much uncertainty associated with these numbers.

Let me give you an example. Let's suppose there was a situation where there was one person here and one person here. That was all we had, and this is how it came out.

Well, now we have an infinite association and ratio scale, and it looks great. But, of course, any statistician looking at it would say even if this was a perfect experiment and this thing had no effect, this is just a coin toss. If one of these people was going to get the disease and the other one wasn't, it was just a flip of a coin as to whether they ended here or there. It was randomized — randomly assigned exposure.

So that kind of uncertainty is addressed by the size of the numbers. If you have much larger numbers, like if you have 30 cases, then you are outside that realm where now it's clearly explained away by chance.

Q: From a methodological perspective, are there examples in the epidemiologic literature of situations where the association was not precisely quantified but conclusions about the causation were reached?

A: Yes.

Q: Can you explain to the Court what some of those examples might be?

A: My understanding, not that I'm an expert in the Thalidomide history, but my understanding of it is that was an example similar to this situation. The evidence became so overwhelming because it was so incredibly rare to see this condition in general, and then suddenly

you have an outbreak, many, many cases coming in. And every time you investigate those cases, you find this exposure.

And the exposure of this drug that's being given — it's easy to identify that it was present, compared to a lot of things like a gene perhaps.

Q: Are there also other things like Thalidomide?

A: Yes, I mean there are examples — again, outbreaks where drugs were so strongly associated with a condition that was very rare, and suddenly there's a whole flood of collections of case reports. And again, there's consistently this one factor associated with them.

This has happened most recently, in an ongoing litigation that I'm involved with as a plaintiff expert, and so you could consider this prejudice. The issue is the relation of intra-articular pain pumps and injection with using them to inject Novocain and Epinephrine in the shoulder, and the occurrence of chondrolyses that has the same kind of property.

Q: I take it there's other examples beyond even those two?

A: Yes, there are lots of examples in the literature.

Q: The Court has already seen this. To clarify, I don't believe you were here. We showed this to Dr. Toscano. But are you familiar with this article that appeared in 1962 in the *Journal of the American Medical Association*?

A: Yes.

Q: Is the *Journal of the American Medical Association* a highly regarded journal?

A: In some quarters, yes. I'll just add the general comment. It's just like all these articles. Just because it's peer reviewed doesn't mean that a lot of junk doesn't make it through and into them.

Peer review has got a lot of random noise in it, too. Who they send it out to could be two people who were too busy that weekend to look at it closely, or it might hit some really, really sharp critics. So they are not 100 percent, no.

Q: Let me read to you, turning to page 1110 in this article. It says, "Thus between November 20, 1961, and January 1962, the

circumstantial evidence rapidly accumulated in different parts of the world, which indicated that Thalidomide played an important role in the production of phocomelia."

Is that consistent with your understanding of the history of Thalidomide and limb reduction defects, how they were discovered?

A: Yes.

Q: And again, we have already shown the audience today some of the pictures illustrating the nature of those injuries.

Are you familiar with what are called the Bradford Hill considerations for organizing evidence regarding causation?

A: Yes.

Q: And the audience has already seen those.

Just to make sure. Is that list of nine considerations, is that your understanding of what the Bradford Hill considerations are?

A: Yes.

Q: Could you tell the Court your opinion about how the Bradford Hill considerations should be used in the analysis of a possible causal relationship?

A: Well, I think they are very good for organizing evidence that you would want to look at regarding the putative relationship in the study, the relationship between the exposure and the disease.

So you can look and ask about what kind of evidence is there regarding strength of the association and to the extent to quantify how uncertain it is. Similarly for the consistency, specificity, so on.

It's not some absolute like natural law. It's a system that he came up with that he found useful. And I find it very useful, too.

It's kind of out of sync with the type of so-called "modern epidemiology," which is the name of the textbook on which my name appears. Modern epidemiology starts with the criticisms of Hill's view, not so much as a classification scheme, but hammering the point which he made himself that none of these is a necessary condition, except perhaps temporality. And they all don't have to be satisfied to reach a kind of conclusion.

But when you come to a situation that looks like an outbreak investigation in this kind of situation, it really does help organize thoughts. Some of them, like coherence, analogy, and plausibility are

hard to separate, but the earlier ones can be given very precise meanings.

Q: Now, you can tell from the title of his article, "The Environment and Disease: Association or Causation?" that Professor Hill was starting with the premise that there was an association that had been determined. And then the question was whether the association would further lead to a conclusion about causation. Do I have that right?

A: I think so.

Q: And does the association that he's talking about have to be a quantified association, or can it be the kind of association that we have seen in this case?

A: It can be the kind that we have seen in this case, yes.

Q: Now, let me move on here.

How does the Thalidomide in birth defects situation, compare with the polystatols and photoneuritis?

A: Well, as I understand them both, these parallel. We don't have a formal epidemiologic study in either case. We have this sudden outburst of case reports that seem to be when you follow them up. If you follow them to the extent where you really make the determination, you find polystatol.

Just like with the phocomelia. When you follow up the case reports, you found Thalidomide. This was something that was infrequent before, so incredibly rare before the introduction of this substance.

Q: And in this particular case, focusing on the polystatols and photoneuritis, the evidence for you is strong enough to reach a conclusion more likely than not polystatols caused photoneuritis. Is that correct?

A: That's right.

Q: I would like to move on to Mr. Schuman's case, again with all of our caveats especially about getting in the area of case specific causation.

And to begin with, what is your opinion about a relationship between AlphaSoleCure and photoneuritis?

A: In general?

Q: Still in general.

A: Well, given that we see from all the data about the polystatols it appears likely that they can cause photoneuritis, then the AlphaSoleCure could. And then it's just a question of at what rate it does versus the others.

Q: If a patient presented with photoneuritis was taking AlphaSoleCure only, which is not our case here, would you say that the drug had causally contributed to the disease?

A: I would bet on it. That's what I mean by more likely than not. More probable than not. I would say I bet the drug was sort of a trigger.

Q: And the same, I take it, would be true with a patient who took GammaSoleCure only but had the disease. Is that right?

A: That's right.

Q: Our situation here is a little bit more complicated. So I would like to explore with you what the causal role was for both of these drugs, given that Mr. Schuman took both of them.

And again, you understand that he took the AlphaSoleCure for eight months and the GammaSoleCure subsequently for three months. Is that right?

A: Yes.

Q: Given those facts, is it your opinion that AlphaSoleCure was a substantial contributing factor to Mr. Schuman's photoneuritis?

A: Again, here I would bet that it would, meaning it's more likely than not for me. That's what the phrase means to me.

Q: But it was more likely than not a substantial contributing factor to his photoneuritis then. Would that be your opinion?

A: More likely, yes. With that phrase in front.

Q: Now I'd like to follow up with a few questions about Dr. Toscano's report.

He suggests that it's necessary to know the mechanism to reach a conclusion about causation. What's your response to that suggestion?

A: That's ridiculous.

Q: Could you expand a little bit on "ridiculous"?

A: Not only do we have the Thalidomide example and examples of the side effects. We also have aspirin, where there's no question by 1900 that it worked. It was being marketed for many generations before really some good idea of how it worked came about.

People were vaccinating in 1800, doing vaccination, and they knew it prevented small pox. They had no idea — they were still a century away from having a clue about our work, creating immunity, whole immune system, viruses, and all that sort of stuff.

So throughout history people figure out this causes or prevents that — prevention just being the mirror of causation — without having any idea of how the mechanism worked, what the underlying mechanism was.

And today in medicine that still continues. Some very popular drugs (like Viagra) have been implicated with visual disturbances. They really only had theories and not really good ideas how they worked when they were approved.

Again, no mechanisms there.

Q: Isn't it correct that, in fact, with Viagra the beneficial effect was discovered by accident in the course of monitoring the use of drugs for something else?

A: Correct.

THE COURT: Somehow I think we're getting afield again.

MR. BLACK: I agree, your Honor.

Q: Let me move on.

Dr. Toscano has also suggested that an epidemiological study is required to reach a conclusion about causation. What's your response to that point?

A: Again, it seems ridiculous, especially if by "epidemiologic study," as people often do, they mean a formal epidemiologic study where people organize a study, maybe provide for funding, go out and collect data, and so forth. That's often what people seem to mean.

And when they say that, again that's ridiculous. So many things were discovered and went into use without that much effort.

Q: Finally, in Dr. Toscano's report, he's written that terms such as contributing cause or substantial contributing factor are not scientific terms, not the sorts of terms that scientists would use in their ordinary discussions with each other, in their ordinary discourse. Do you agree with that statement?

A: No, I disagree.

Q: Again, could you expand on that point, please?

A: First of all, we use concepts. Contributing cause isn't in itself the jargon that's used, for example, in modern epidemiology. But there are equivalents to the more formal terms. Just like we don't use but-for in modern epidemiology, you can see the same idea right there with potential outcomes.

We don't use contributory cause, but we use the idea of component cause, which means it's informal in a more precise logical sense. It's again the scientific analog.

And if people in a discussion referred to contributory cause, they would know what you mean. They mean that this is a piece of the pie.

And literally there are these pie diagrams in Chapter 2 in *Modern Epidemiology* and in other textbooks. You can find them as well in articles showing all the pieces contributing together. And when they all come together finally, the disease occurs or is inevitable.

So the concept of contributory cause is clearly there formalized in the idea of component cause. And it's a well-understood idea.

Now, to go to the next one. Substantial. That's a little more vague. "What do you mean substantial?" That might mean in terms of frequency with which it acts or the number of sufficient causes in which it acts. So that one would require a little more commentary.

Q: Come back to this case.

It's your opinion that both the Alpha drug and the Gamma drug were contributing factors to Mr. Schuman's photoneuritis. Is that correct?

A: Yes.

Q: And it's your opinion that both are substantial —

A: Now, wait a minute. Again, I would say more it's more likely than not. I don't want to —

Q: Yes. Let me rephrase the question.
It's your opinion that more likely than not both the Alpha drug and the Gamma drug were substantial contributing factors to Mr. Schuman's photoneuritis. Is that correct?

A: This is the part where the script and I have a problem.

Q: Yes, for purposes of today.

A: Yes, for purposes of today.

MR. BLACK: No further questions.

THE COURT: Nothing further?

MR. BLACK: No, nothing further.

THE COURT: All right. Cross-examination.

—o0o—

CROSS-EXAMINATION BY MR. SMITH

—o0o—

Q: Good afternoon, Dr. Greenland. Let me go back to address the portion of your testimony dealing with general causation that Mr. Black questioned you about earlier.
Would you agree that — and I think you said this — science has not yet identified a mechanism, biological mechanism, by which polystatols may be causing photoneuritis. Correct?

A: Yes.

Q: And that although Dr. Vishun, in one of his publications, suggested that polystatols could cause photoneuritis by affecting an

enzyme involved in vision, would you agree that that is not something that has been established more likely than not to be in fact the case? It's a suggestion, it's a hypothesis at this point, something that has not been established. True?

A: Yes.

Q: Let me ask you, if all you had in this case was the clinical trial data on AlphaSoleCure, that's all you had, you didn't have any information on Beta or Gamma, would that data be strong enough for you to determine or conclude more likely than not that the AlphaSoleCure was a general cause of photoneuritis?

A: You would have to remind me what that data looked like. Can you do that? All we had was the one event in the Alpha?

Q: All we had was the one event in 2,660 patients and zero in placebo. We didn't have any of the other information where the rates are significantly higher.

In that circumstance, under that hypothetical, would it be your opinion that more likely than not Alpha was a cause of photoneuritis?

A: I would not have that opinion here, no.

Q: And would you agree with me that in the limited data that's available, the associations with Gamma and Beta were significantly higher for this particular result than they were for Alpha?

A: Yes.

Q: And you recognize from the information that's provided in the record that both Beta and Gamma were different enough in some way to warrant their own separate patents. Is that correct?

A: Yes.

Q: Do you know in what ways they differed chemically or biologically?

A: No.

Q: Do you know whether those differences — let me state it differently.

Would it be fair to say that not knowing what those differences might be, you wouldn't be in a position to express an opinion as to whether or not they could affect the likelihood that those two drugs could cause photoneuritis and Alpha might not?

THE COURT: Can you try that question again?

THE WITNESS: You lost me.

MR. SMITH: I apologize for garbling that.

THE COURT: Sometimes they just sort of take off under their own power.

MR. SMITH: Yes, they do.

Q: Given that you do not know the differences between the chemical structure of Beta, Gamma, and Alpha, would it be fair to say that you aren't in a position to say that those differences might mean that those two, Beta and Gamma, could cause photoneuritis and Alpha could not?

A: Well, I could make some bets on it.

Q: And how would you go about determining how to wager on that?

A: That they are not completely distinct chemicals. And the evidence is that they are acting along the same or related pathways. And, therefore, this makes it now suggestive — it's an interesting problem to me, academically.

If you strike the two middle rows, that's how you start it.

At one point you only would have seen this row and last row. You would say, "Hmmm. That's just one event that could have been sporadic and it's very rare. We better keep an eye on this sort of thing, just in case."

And then along come these two. And here's two related chemicals. It's not the differences that are my concern, it's their similarities that are my concern. And they are being used for the same therapeutic benefits.

So they clearly can have similar effects. In fact, they are being used to treat the same disease in the same way.

So that would suggest that they could now have similar adverse side effects. And indeed, now we see that for these, which are even more

potent supposedly as a cure with Gamma requiring fewer treatments, the adverse event rate is much higher.

Now this carries over and informs this and says, "maybe that one occurring up there wasn't a fluke after all." Some more evidence of it not just being a fluke.

Q: If I recall correctly your answer, you said that they could — what you just postulated could be an effect — but you didn't say it probably is?

A: Correct.

Q: And also just to make sure there's no confusion.
This chart shows a difference in terms of the relative adverse rates not in the efficacy of the drugs to treat Sole's Foot.

A: Correct.

Q: Dose-per-dose basis.

Doctor, do you agree that it's not uncommon to find strong associations or correlations between events when there are actually no causal connections, that is, where the events may be explained by some other third activity that's correlated with the two that you studied?

A: We call that confounding.

Q: That's not uncommon in the real world. Correct?

A: That's correct.

Q: And one of the things that your discipline is designed to address is how to distinguish confounding situations where there isn't any real causation despite the association or correlation, from those where there is actual causation in addition to the association or correlation. Is that correct?

A: Correct.

Q: In this case, those kinds of studies were not done. Correct?

A: That's correct.

THE COURT: That's kind of like kids who drink milk and wound up smoking marijuana?

THE WITNESS: Right. I guess.

Q BY MR. SMITH: Would you agree that in this case, to this point in time, no statistical analysis has been made of the data that's available to evaluate error bars or correlation coefficients, the sort of statistical analysis that tries to get at the strength of correlations themselves. Correct?

A: To me, the question that is more to the point is, has there been an analysis which has attempted to identify some third factor that could have produced this relation without any effect of this drug itself. And for a situation where, going back to what you asked about, the first row of boxes versus the last row. You say that could very easily be just a fluke. And that would mean some kind of confounding.

But if you get down to the Gamma row, now it's getting to the point where it gets hard to come up with something. And nobody at this point has come up with something that's an alternative.

Q: That's in the context of where we really don't know what the significant differences are between these drugs. We know they have been patented as being different, but we don't know anything about the significance of those particular differences, their ability or potential to cause photoneuritis. Correct?

A: I was looking at Gamma versus placebo. I thought you were talking about that. So maybe we're on a different page.

Q: I'm sorry. But just to go back and sort of complete the loop on general causation. I understand it is your opinion that there is enough evidence here to conclude that polystatols, including Alpha, cause photoneuritis.

A: Again, I would modify that. More likely than not, I would bet.

Q: I appreciate that distinction. But you agree here we don't have epidemiology studies or background rates on photoneuritis, to establish that the rates have actually gone up or how much they have gone up over time. Correct?

A: Again, we have some literature evidence giving the frequency with which the condition was reported in the literature. And there's some controversy about that, of course.

Now, I want to raise one point about this, whether that's an epidemiologic study right there. There are people like me who take a very liberal view of inclusion. This is an epidemiologic study. We can criticize it on a lot of grounds. I don't have to go into every detail.

There are others who have a much, much higher standard of what they will call an epidemiologic study, going to the point of even saying it has to be designed to look at this problem. But that's not a universally-adhered-to view.

Q: You would also agree, I take it, that at this time we haven't done enough analysis to know that there might not have been other changes over the last few years that might equally correlate with these cases, but might be independently causing them, that is, independent of the taking of the polystatols?

A: But that wouldn't be sufficient to explain this. Not only would the exchanges have to take place, but they would have to have been concentrated in the people who happen to get Gamma.

If I look right at that table.

Q: That's something that's quite possible, isn't it?

A: Well, is it? I don't know. Nobody has come up with an alternative.

Q: At this point we just don't know?

A: Right.

Q: Let me turn to the specific causation opinions that you offered here today to make sure that I understand them.

As I understand it, you indicated that, in your opinion, both Alpha and Gamma could have contributed causally to Mr. Schuman's illness. Is that correct?

A: Again, more likely than not.

Q: Excuse me. And you said that we didn't know which did, and, therefore, what we could say at most is each contributed to the probability that he would get the disease. Correct?

A: Please repeat that.

Q: I understood you to say that we didn't know which of the drugs may have caused it, but what we could say is that each contributed to the probability of him getting the disease?

A: Yes.

Q: Now, you agree with me, don't you, that saying something has a probability of causing something is not the same thing as saying it caused it?

A: Yes.

Q: An analogy I might use is that I buy 100 lottery tickets; each one creates a probability that I will win. But if I win, only one of them caused me to win the lottery. Correct?

A: Or caused your sudden wealth.

Q: So to state that something contributes to a probability or possibility of an outcome isn't to say it actually causally contributed it. Correct?

A: In general it might. For example, if you had a relative in the lottery office who was making sure.

Q: I understand. Let me ask you this. I understand that you believe that Mr. Schuman's exposure to both of these drugs was causal. Let me ask you this. As you use the terminology —

THE COURT: I want to be clear. Was it causal or was it contributing to the probability?

THE WITNESS: Well, let me explain this. For me, in all these causal questions, in the way I conceptualize these things and describe them in many published articles, it's all about probabilities ultimately. It's just that when we drop the word "probability," we are in a situation where our probability has gotten so close to 100 percent that we are not even making the distinction.

This is also part of my background in philosophy. This is part of the old idea that, for all you know, your brain is in a jar somewhere and all of this is being fed into you. "The Matrix." Right?

THE COURT: There are people who have said that.

THE WITNESS: Right. But for all practical purposes, you are not even going to bother to put a positive number on the probability that your brain is in a jar.

And so, but ultimately when we get to certain things, the probabilities for me are not anywhere near ninety or even eighty percent.

When I say more probable than not, that could be just as simple as saying it's over fifty percent. And in a case like this I wouldn't put it much past. But I had to put down a dollar one way or the other. I've got one side or the other. I'll put it down on the side that, yes, it's a contributory cause.

Why is that?

Well, I look at the numbers. It comes right back down to look at the numbers, given that background. We wouldn't have expected any cases in those people in the ordinary course of events if these polystatol weren't somehow connected to the event.

And there's evidence that the polystatols can somehow interfere with vision in some way. And, therefore, I reach this betting conclusion. I'm not going to bet my life on it.

Q BY MR. SMITH: Let me ask you to place a different bet. If you had to bet on whether it was the Alpha or the Gamma, what would you say the relative probabilities were for each as being more likely than not a cause?

A: Well, I would definitely put it higher on the Gamma considering them separately as general causation, in general. But the evidence on the Gamma indicates that they are not independent because the evidence on the Gamma contributes to probability on the Alpha. They are correlated hypotheses.

In other words, let's suppose that we find out tomorrow somebody has done some horrible, unethical clinical trial where they randomize Gamma to an enormous number of people, looking at vision symptoms, and they found that indeed this is thirty-fold or more, it's an enormous relative risk for it. That would up my bets on Alpha because it's a related compound.

In other words, I'm looking at the similarities again, not differences. It's a related compound with related therapeutic effects.

Q: Let me put this in some but-for terms or terminology as you referred to it before. Are you able to say it's been established more likely than not that Mr. Schuman would not have gotten his photoneuritis if he had not taken Alpha and only taken Gamma for the three months when he took the drug?

A: Again, that would be my bet.

Q: Can you explain how you come to that conclusion that if he had not taken it, he wouldn't have gotten sick?

A: Because it's so incredibly rare without taking one of these drugs. The Sole Foot he was being treated for is so incredibly rare I wouldn't have expected to see him get this.

But then he takes this drug where it is clear that the adverse rate is not zero. The adverse rate is not zero in that group.

Now, if it was just Alpha alone and we hadn't gotten the information on Beta and Gamma, I wouldn't be in as much of a betting mode for that as I am. But I just say, "Look, look at the numbers. What would you do?" If you were given the choice of taking that cure, you would accept that risk if you saw it.

Q: Let me ask you because you raised this point, I think, indirectly in some of your prior testimony. You talked in response to Mr. Black's question about how you go about making these determinations in the absence of sort of a checklist of criteria. And you talked about, among other things, making assessments that were sort of risk-benefit assessments, the sorts of things that government agencies do, Food and Drug Administration, EPA, and others. They make these sorts of judgments as to when, from a societal perspective, we decide maybe the risks don't justify the benefits that are entailed.

And they apply what we refer to as precautionary principle. Sort of erring on the side of if we don't know, then in most cases we'll maybe be extra cautious and won't have the exposures.

Would you agree with me that that kind of assessment is not the same thing as saying that in fact there is causation? Just because you might want to avoid a risk doesn't mean that if you don't avoid the risk, it actually caused the injury?

A: I would agree with that, yes.

Q: So the fact that you might avoid these risks if given a choice doesn't mean that simply because you incur them, they actually causally produced the result?

A: That's correct.

Q: And in this case the data indicates to you, as I understand it, that of the two drugs that Mr. Schuman took, the risk was far greater that he would get the illness from the Gamma than from the Alpha?

A: The problem is that I can't separate them. Again, going back to your boat analogy, maybe it was the combination of the doses. Maybe the Alpha, even though it contributed a small amount, it's what put him over the edge. But-for the Alpha, he wouldn't have gotten it.

But-for the Gamma, he wouldn't have gotten it seems more clear, but it could also be that. Again, also with the hole in the boat, if it was the other mechanism where just one pellet got through and put the hole and it was a slow leak, I can't be sure that it wasn't with the Alphas.

Q: But you also would conclude in that situation it would more likely have been the Gamma. Correct?

A: If it was only one of them. But they might both have contributed.

Q: And it is might or maybe, not more likely than not. It's a might or maybe. Is that correct?

A: That's correct.

Q: Just one last question on this, Doctor.

Are you able to say that if Mr. Schuman had taken only the Alpha drug for the eight months and not taken the Gamma, he would not have gotten photoneuritis?

A: You're asking — please repeat.

Q: In a hypothetical situation where he had taken only Alpha.

A: Took the amount given?

Q: The amount given here.

A: Okay.

Q: With the risk associated with that and if he had not taken any Gamma at all, would he still more likely than not have gotten sick?

A: I can't comment on that. I don't know.

MR. SMITH: Thank you very much.

Q: Actually, I've been advised by my co-counsel that there is one topic I wanted to cover with you. You have described the methodology or the analytical process you have gone through in deciding that there was general causation here with respect to Alpha, Beta, and Gamma. And you have explained how it is difficult to articulate precise criteria for making that sort of an assessment.

Have you ever undertaken or known anybody who has undertaken an evaluation of verification through subsequent data or subsequent epidemiology, to validate or verify the judgments made in the way you are making here today that turned out to be accurate?

A: I think that's done much of the time. For example, take Thalidomide. Action was taken very early. It was recognized without all the formal epidemiologic study.

And over time people continued to study it because the drug, as it turned out, still had useful, therapeutic benefits precisely for the mechanism that was causing deformities. It turned out to have potential as an anti-cancer agent.

Q: I think there's been agreement there are situations where that kind of judgment has been made and made correctly. My question is intended to get at the issue of whether or not a number of such decisions have been evaluated to see whether all of them, or only a portion of them, or how few of them turned out to be validated subsequently.

A: People have attempted to do studies like that, yes. They are very, very controversial because of the selectivity involved and the way they do the analysis. This is at a level of what might be called meta-analysis or even above meta-analysis, for those who have heard those terms. Some people have called them somewhat derogatorily the term mega-analysis where the technique's — there's just no established method

— sort of the "Wild West." There's no established techniques and methodology.

People have been attempting to do this. But that is in the systematic way I think you were trying to describe. But it's a highly, highly controversial area in its infancy. I would say that. That's my view of it.

MR. SMITH: Thank you very much.

MR. BLACK: Your Honor, if I might. I have a few questions on redirect.

THE COURT: Redirect. Mr. Black.

MR. BLACK: Thank you, your Honor.

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REDIRECT EXAMINATION BY MR. BLACK

—o0o—

Q: Just a few points, Dr. Greenland.

Mr. Smith asked you about the article by Dr. Vishun about mechanism. Do you recall that?

A: Yes.

Q: Do you rely on the Vishun article in any way for the conclusions you have reached in this case?

A: I would say that it influenced my opinion.

Q: If there had never been the Vishun article, would your opinion be any different?

A: No, I would still give the same, more likely than not, opinion.

Q: Now, Mr. Smith also showed you this information still on the screen from the clinical trials in terms of the number of adverse events.

I would like to show you Table 4, which includes the adverse event reports that came in outside of the clinical trials.

Am I correct that after a drug goes on the market, there is a system where if an adverse event occurs, a doctor can report it to the FDA?

A: Yes.

Q: So this would represent adverse event reports that came in after the drug was on the market.

If you look at the Alpha Drug Photoneuritis Reports, in 2008 there were seven. Is that correct?

A: Correct.

Q: And in 2009 it went up to nineteen. Correct?

A: Yes.

Q: 2010 it went to thirty-two. Is that right?

A: Right.

Q: If I do the math right, that's fifty-eight total reports of photoneuritis with the AlphaSoleCure drug. Is that correct?

A: Yes.

Q: And for GammaSoleCure, it's even higher. It goes up to 235. Is that correct?

A: Yes.

Q: Now, on the specific causation, I'm not clear whether this question went to specific causation or general.

Mr. Smith asked you a question about the error rate, whether there was some determination of the error rate regarding the methodology you used to reach your conclusions.

Can you really accurately calculate an error rate for the kind of process that you went through?

A: Not at this time. That's part of the controversy I have alluded to. How should you and could you calculate an error rate?

Q: Are you familiar with what have been called the *Daubert* criteria for scientific evidence?

A: In general vague terms, not in precise.

Q: Error rate happens to be one of them. Let me go through the others and see if they are applicable to this case at all.

One is the testability of a hypothesis and whether or not it has been tested. Would you consider whether your hypothesis in this case has been tested adequately for you to reach a conclusion?

A: Again, this is another area of controversy about the issue of testing in methodology and what form it should take and what it means. This is extremely controversial in the science itself and has been for decades since the concept was really introduced formally.

But if I could explain what the problem is here. There's a pure mathematical model, an idealized case, where you would calculate an error rate for methodology by saying, "Here are all the cases where we know this was indeed a cause; and here are all the cases where we know this wasn't a cause at all."

And this is an oversimplification because I'm leaving out strength here just to make the point.

On this two-by-two table. It would be a different two-by-two table, another one, but maybe a few weeks later in epidemiology.

So maybe if I can draw that table.

It's a different table.

Cause.

Not cause.

And the method.

Then we have on this declared cause.

Declared not cause.

So now we can talk about how often, if we looked at all those, what are the predictive values. That's really the bottom line.

We say how often was it that when we declared a cause, it was actually not a cause. And how often where we declared it to be not a cause, it was actually a cause.

You look at error rates this way. How often among true causes do we declare them a cause? That's the sensitivity. And how often among those that were not causal, do we correctly declare them not a cause? That's called specificity.

But in the end, in practice, it's the predictive values that determine how well you're doing.

The problem is that to construct this table and get the predictive values out correctly and to get anything out correctly, we have to be able to successfully classify the hypothesis or the asserted relations between "cause" and "not cause."

People claim that many things are settled. We have things like smoking and lung cancer which we, by and large, can now classify. Even the tobacco companies have given up trying to argue it. It doesn't belong right here.

And we have other things where people have given up trying to argue that something doesn't belong here, like between some severe health risk and a few cups of coffee.

We have many, many other things, such as vitamins, where it's not clear where they belong. And in the vast majority of cases that I see, both controversies in the scientific literature and then coming into court, we really don't know.

There are people who claim they've got estimates of these predictive values of these kinds of error rates published in, like, JAMA. And we see how they have fudged things. Maybe they don't intentionally, but they have made methodological assumptions which are quite dubious to try and force things into the "cause" or "not cause" category. This is the whole game.

The problem is that in the end there's too much stuff that you really need a third row here. Except this should be expanded to most of these situations, to something very large.

The biggest numbers are right in here, so we can't calculate the error rates of methodologies for these kinds of topics, like a lot of drug side effects. And even sometimes they're beneficial effects.

Clinical trials —

THE COURT: I suggest we try to confine this a little more to question-and-answer motif.

MR. BLACK: I will move along and not ask a follow-up question on that.

Q: With regard to the peer review, the methodology that you have used, relying in fact that there have been adverse event reports, has that been used by others in the peer review literature?

A: Yes.

Q: And would you say that the methodology that you followed in this case is generally accepted among epidemiologists?

A: I would say that the statistics and epidemiology fields in which I am qualified are split about many methodologies.

Are they generally accepted? People will come in and say, "This is generally accepted, and that's generally accepted." And I hear that, and I say, "No, the field is split maybe 60/40, 70/30, maybe 50/50."

So what do you mean by "generally accepted"? You can find plenty of experts with good credentials who will say, "Yes, it is," and others who say, "I don't accept that. I think it's rubbish."

Q: In this case, the use of adverse event reports as you have done in reaching your conclusions about the polystatols, would the majority of epidemiologists consider that an appropriate methodology or not?

A: I would say a large number would. You would have to do a sample survey, scientific survey, to know whether it was a majority or minority. Nobody has done that.

Q: So it's a question that can't be answered given what we know now?

A: Given what we know now.

MR. BLACK: No further questions, your Honor.

THE COURT: Thank you.

Recross?

MR. SMITH: No questions, your Honor.

THE COURT: Thank you.

I have a couple of questions.

As I understand your testimony, your belief that Alpha was a contributor is enhanced by your thought that Gamma was a contributing factor. Is that correct?

THE WITNESS: Correct.

THE COURT: Assume with me for a moment that there had been a single exposure to Alpha a year ago. What would it take to exclude Alpha as a causative factor, in your view?

THE WITNESS: I would want to see if I had gathered that data.

THE COURT: I'm sorry?

THE WITNESS: If I had enough resources, I would gather the available data to see what the typical lag periods are between the Alpha therapy and the outcome of the photoneuritis. If those were always within a year and this happened a year later, that would definitely drastically reduce my confidence in the hypothetical.

THE COURT: So latency might make a difference?

THE WITNESS: Absolutely.

THE COURT: Okay. When it comes to determining a contributing cause, whether you would be more inclined to put a dollar down on one side of the table or another, are you talking about one standard deviation? Are you talking about two standard deviations? Are you talking about it just seems more likely? Try to define that for me.

THE WITNESS: None of this is quantified enough to put things in terms of standard deviations.

THE COURT: But I'm going to be forced to ask a jury to determine whether it is more likely than not — that is the standard I will be required to apply.

I guess I'm trying to see where your calculus fits within moving from the scientific grid to the legal grid. Where are we in your view?

THE WITNESS: Well, all I can say is where I am.

THE COURT: I understand. I get to be the judge. That's my job.

THE WITNESS: All I can say is this is my opinion. I can offer you my opinion. You know my background. You know who hired me. All these factor into it for you, I presume, and would for me if I were in your position.

This goes far back, a long ways back, centuries back, with old statistics before there was standard deviation, probable error. There was this concept of P value. Some of you have heard that that concept goes all the way 300 years in one form or another.

THE COURT: I was already a lawyer then.

THE WITNESS: And they already knew that tobacco caused death from lung cancer.

THE COURT: I had a tobacco farm.
Let's focus on our case, if we could.

THE WITNESS: Yes. Well, but I was focusing on the question you asked on the methodology of saying, well, look where I am? Am I probably on this side of the null or that side of the null? Which side am I on? Which side do I place the dollar down?

And the answer was, basically, I'll put it on the side where the weight of evidence seems to be tipping towards.

This is not, I tried to emphasize, like a ninety percent bet. This is a bet on the equivalent of, like I said, a beer or something. This is a bet on the level of it looks to me like this is a causal relation at this point. I would bet on it.

It doesn't mean that tomorrow some refutation might come back, "Oh my gosh, this is all because of the way they pick people to get this therapy."

But what are the other causes? In fact, it's not just the data that the defense showed, but the data that the plaintiff showed, the plaintiff's lawyer. All of a sudden you get this burst of case reports. That to me is absolutely crucial.

THE COURT: Let me try one more. Assume for a moment one exposure to Alpha and fifty exposures to Gamma.

THE WITNESS: Yes.

THE COURT: Would you still be of a mind that the exposure to Alpha was causative?

THE WITNESS: Well, it would definitely be a case where it would be weaker, much weaker, for me.

THE COURT: Okay. I thank you, Doctor.

MR. SMITH: Your Honor, one follow-up?

THE COURT: Yes, sir. I apologize; I would have otherwise asked.

For those of you who are not familiar. When a judge usually asks questions, it re-opens the examination so the lawyers can try to straighten that idiot out.

MR. SMITH: Certainly not my purpose.

THE COURT: I know, certainly not.

—o0o—

RECROSS EXAMINATION BY MR. SMITH

—o0o—

Q: Doctor, just to help me clear up some confusion I have.

Tell me if I'm incorrect on this. My understanding is that in the dialogue you just had with his Honor, you were indicating that the data you saw, particularly the data that Mr. Black showed about the increased reports of photoneuritis with Alpha later on and the fact that photoneuritis was also coming with Alpha and Beta, increased your feeling about causal relationship between Alpha and photoneuritis. Am I correct so far?

A: Yes.

Q: It had been my impression earlier that that analysis strengthened your view that Alpha could be a general cause of photoneuritis. Correct?

A: Correct.

Q: When it comes to specific causation, as I understand it, you have acknowledged that we don't know the mechanism, the biological mechanism, by which photoneuritis is caused by polystatols even if you assume in fact they are caused by them. Correct?

A: Correct.

Q: Am I correct that there are biological mechanisms by which various events occur not through additive exposure, but rather because of the probabilities increasing with each exposure like the purchase of lottery tickets and things of that sort. Correct?

A: Yes.

Q: In this case we don't know that it's not the lottery ticket mechanism approach. Correct?

A: Correct.

Q: So would it be fair to say in this case we don't know that in fact the exposure of Alpha to Mr. Schuman actually ended up being in the causal chain of his disease?

A: We don't. But, you are using these terms with certainty. We certainly don't know.

Q: I didn't mean with certainty. More likely than not.

A: Yes, in that case, at some point it becomes too ambiguous for me to say anything.

MR. SMITH: Thank you.

THE COURT: Anything further, Mr. Black?

MR. BLACK: No, your Honor.

THE COURT: Thank you, sir. You may step down.
I take it, counsel, each side rests?

MR. BLACK: Plaintiff rests, your Honor.

MR. SMITH: Defense rests, your Honor.

THE COURT: Thank you. Take a break.

(Break taken from 2:19 to 2:48.)

THE COURT: We are back in session.
Showing the prerogatives that judges do, of course, I decided to change things a little.
Mr. Black, are you of a mind to give a closing argument?

MR. BLACK: I believe under the circumstances we should proceed to the panel discussion, your Honor.

THE COURT: Mr. Smith?

MR. SMITH: Ditto, your Honor. I concur with Mr. Black.

THE COURT: This is a rather good approximation of what a *Daubert* motion might be. A *Daubert* motion is a bench proceeding. It is tried only to the judge. There is no jury.

Good Lord, to see this many people in a courtroom, I saw this only about three times in 25 years and almost inevitably in a really huge criminal case when the verdict was coming in. But in a *Daubert* case you can fire a cannon in a courtroom and not hit anybody.

But being a bench proceeding, there are seldom opening arguments and almost never a closing argument. The judge would have been provided a brief by each side covering all of the material.

It would normally be probably not as long as this proceeding. The lawyers would then present whatever they needed to present, and they would ask me to make my ruling. I would go into one of my trances and come up with a ruling.

So would you like a ruling? I'll try and give you a ruling.

The first thing you do is you take a look at *Daubert*. You need to carefully recognize that these are not exclusive categories.

So did either of them provide testability? No.

Was there peer review for their opinion? No.

Do I know the error rate of the opinion that they expressed or the methodology? No.

And was there a scientific acceptance of their view? Well, each accepted their own view.

By the way, for those of you who haven't taken the Evidence course, scientific acceptance, which is one quarter at least of the factors, is the old *Frye* test based on the *Frye* case.

So to whatever extent we have amplified it, all we've done is brought in a few more factors for the *Frye* test.[1]

So we look at Bradford Hill consideration, which has never been accepted by the United States Supreme Court.

Strength of association. Well, there's some association here.

Consistency.

Specificity.

[1] Frye v. United States, 293 F. 1013 (D.C. Cir. 1923).

Temporality.

In many cases, there was some sort of relationship during the time that it occurred.

Biological mechanism. Whatever the heck that means. I have no idea what that means, but nobody testified about it.

Plausibility. That's not really much of a factor.

Is it possible? That's plausible.

Is it coherent, and was there any experiment? And the answer is no.

Okay, so now the punch line.

This would be a very tricky case. The plaintiff would have a very hard time because the claim is not whether the product could have caused it; rather, it was this Alpha version of the product, which had obviously a much lower occurrence rate, could have caused it.

It was very interesting to hear, and I was fascinated by the argument, that the greater strength of the subsequent products, Beta and Gamma, strengthened the presumption about the earlier one, which would have otherwise seemed less likely.

I probably would have allowed them to testify. This was a contrived set of facts, and you have to deal with that.

It seems to me that the proof on this case is going to be very difficult. If you want the test and a rule, experts cancel each other out. That is the legal rule on experts.

They each have bulletproof credentials. They each are brilliantly qualified. Each has got a doctorate.

And, as I pointed out to somebody earlier, you can get somebody for a sufficient amount of money who will testify and be able to prove that I am my own grandmother. That is based on twenty-five years of experience.

So, with that, I would say that I would probably admit both.

That is on this peculiar case.

I have on several occasions struck experts. It's a weird thing to do because you kind of know this is going to go on their record.

This stuff goes on the Internet in half a second. And when you say this person is not qualified to testify as an expert, you are putting a real kiss on their record. Nobody ever talks about that.

But if somebody may espouse a position that a judge finds unacceptable or one that they would not permit, you realize that you are going to paint them in a certain way, and they will be cross-examined on that in further testimony for the rest of their life or maybe no longer be able to testify.

Nobody has ever mentioned that other than judges when they talk about it. But it's not part of the literature. But it's an odd place to put a judge, but judges do it. And there are times when you feel you have to.

So that would probably be my ruling.

But with that, more interesting would be the discussion that surrounds it, and so why don't we throw it open.

PROF. IMWINKELRIED: What we're going to do now is have comments by the panelists not only about their role but about other panelists' roles. And then we're going to throw open the floor for questions from the audience so that everybody can become involved in the discussion.

Why don't we go first to Bert to talk about his perspective as the plaintiff's attorney both in general in *Daubert* hearings, and on this one.

MR. BLACK: Well, I certainly agree with what the Judge said about the way *Daubert* hearings are conducted.

There would be expert reports in almost any case. There are exceptions to everything, but you ordinarily would have expert reports, you would have depositions, you would have a *Daubert* motion from one side to exclude the other side's expert or experts, and then you would have a response.

You would at least have those four documents available, four pieces of the record available, before there would ever be a hearing.

And sometimes the court would want to hold a hearing and sometimes not.

Courts will, I won't say often, but they do sometimes rule just on the record.

So this was a little bit contrived and probably went into more detail and was perhaps a little more formal than many *Daubert* hearings in which I have participated.

As to this specific case, we designed this case to get across a couple of points about the application of *Daubert* and scientific evidence more generally.

One point was on general causation. There are judicial decisions and there are lawyers who conduct their practice as if you have to have an epidemiology study in order to establish that a drug causes a disease or an adverse effect, or that a substance caused a disease.

That's just not right as a matter of science.

And when they say "epidemiology study," they don't take a broad view of epidemiology studies the way Dr. Greenland does, where even some of the comparisons here might count as an epidemiology study. They mean a double-blinded clinical trial, something like that.

How could you ever even conduct a double-blinded clinical trial when you have strong suspicion the substance in question, the drug at issue, could cause an adverse effect?

So the point being that some checklist standard, some absolute requirement for a particular kind of evidence in any case, is really contrary to science and ought to be contrary to *Daubert*, although you sometimes see rulings that indicate to the contrary.

And then another issue that comes up, and has not been addressed very much in the context of *Daubert*, is what do you do when you have complex causation situations where there are two suspected causes as we had here, two different drugs. You try to sort out which was the predominant cause, which one should be held responsible. That's both a legal and a scientific issue.

And that's an important point that has not been subjected to much *Daubert* analysis. But we wanted to bring that out as something interesting about the use of scientific evidence.

And I hope that the way we structured this particular hypothetical got both of those points across.

I want to say one additional thing, and this is my perspective on the way *Daubert* ought to be applied. There may be some difference on this.

I think sometimes it's over-applied, that judges seem to require almost absolute proof that you establish a case — not beyond a reasonable doubt, but at least that you met the standard for proof in front of a jury. What you try to do is get your evidence admitted.

And there was an interesting comment from Justice Breyer, interesting that he even made this comment. If you take a look at the second, 2000 edition of the Federal Judicial Center's *Reference Manual on Scientific Evidence* — Justice Breyer wrote an introduction. And in the introduction he tells a story about a famous Nobel Prize-winning physicist who was once asked if a paper was right or wrong.

And this famous scientist's response was, "That paper isn't even good enough to be wrong." In other words, it's so far outside the normal discourse of physicists, we can't even talk about it as right or wrong. It's not physics.

Then Justice Breyer goes on and says, "And that's the kind of evidence that *Daubert* was meant to exclude, the real outliers."

And I think that what you see in some courtrooms is not just excluding the outliers, but things that are within the realm of normal scientific discourse and ought to be admitted.

And that would have been part of the argument if we presented closing arguments here in this symposium today.

With that, I don't know who would want to go next.

PROF. IMWINKELRIED: Why don't we turn to your expert next?

MR. BLACK: I might ask Sander if he could explain why he didn't want to go into some of the specific causation opinions and what he might really think of the causation in this case.

DR. GREENLAND: This case wasn't real, so my opinion on it is that there was no causation because there was no such person, no such disease.

I specifically try to narrow what I will testify about. I try to be upfront about that when people approach me to testify.

I have certain criteria about testifying. It has got to be an interesting case. I have more offers than I plan to take, or would want to. I don't need the money.

But one of the things I try to do is say, "Look, I am not a physician. And so I will not testify on specifics of whether this caused the disease in your patient, person or people, or whatever. I am an epidemiologist statistician. That means I deal with populations and that's general causation, it translates to general causation."

And sometimes I say, "You need to hire, make sure you've got physician experts who will take that step." And sometimes that message is loud and clear and they do that, but sometimes it doesn't seem to sink in. And in the middle of it I'm just going, "Oh."

That's one of the reasons. That's one of the main reasons.

THE COURT: Have you participated in *Daubert* hearings?

DR. GREENLAND: Yes.

THE COURT: How frequently does the judge ask questions in a *Daubert* hearing, in your experience?

DR. GREENLAND: In all the hearings I have been in, in *Daubert* or otherwise, they always ask me questions, yes.

THE COURT: I've never been a *Daubert* expert or an expert subjected to it. The only *Daubert* hearings I have ever seen, I conducted. I now have finally a witness who has been in another one.

DR. GREENLAND: If I can make another comment about it, though. I was very bothered in the pain pump litigation that I mentioned where

they have admitted testimony from a peer-reviewed journal, published studies of this issue which they labeled case series. But from my perspective they were clearly retrospective cohort studies. And they tried to claim they were not epidemiologic studies and tried to denigrate them.

But then they would admit testimony from the defense physician saying, "In my practice I have never seen this outcome."

And that is essentially introducing a study that was not only never peer reviewed, it was never even written up as a study, and no methods were described. It was just some physician based on his anecdotal report of his practice. And that is the same as a study.

If *Daubert* had any meaning in terms of the peer review element and all the other criteria, that should be excluded if we are applying a uniform standard.

PROF. IMWINKELRIED: I had one question based on your interaction, and it was a question to his Honor.

There were times in Bert's questioning of you when you wouldn't give him the answer he wanted. I've heard experienced attorneys tell me that they sometimes do that deliberately on direct examination of an expert in order to demonstrate the expert's independence. This isn't the person who will say whatever the direct examiner wants him to say.

And I was wondering from his Honor's perspective, is that your reaction? Are you saying well, these people just aren't prepared or are you saying this is an exceptionally honest expert who won't say —

THE COURT: The answer is I can't use the term.

PROF. IMWINKELRIED: We want you to be blunt, your Honor.

THE COURT: You don't want me to be that blunt.

I used to be a trial lawyer. That's what I did for a living. And I know when I'm getting greased and lubed.

And when the lawyer says, he bares his breast and he said, "Shoot me," and then the guy shoots him, I know it's not. I've seen this enough times. I'm not real excited about it.

So, you know, it may be a person who's so moved by the virtue of his position that he can't do anything, or it might have been a setup. I'm comfortable with the possibility it is a setup.

PROF. IMWINKELRIED: Why don't we turn to the defense side.

Bob, your perspective.

MR. SMITH: My perspective on *Daubert* is that the most significant thing it provides is a forum, which didn't previously exist, for getting the Court educated before you get in front of the jury on some very complex issues that should end up affecting what is admitted.

In the absence of a *Daubert*-type hearing, you really can't, in front of the judge and jury, try to explore.

But in a *Daubert* hearing you get to go into it, you get to show the judge what's going on and let him or her get a feel for what the issues are and get some confidence they understand the issues of the day.

I think that's the biggest thing from my perspective.

And I tend to focus on the specific causation issues because I think in far too many cases, even where general causation is shown or a good case for it is made, the attorneys — and I think this has been a general failure in a lot of cases where the defense bar really doesn't appreciate the opportunity to really go after specific causation — don't understand in many cases what the experts are really saying.

I think there are tremendous semantic games that go on in these cases where a lot of experts — we tried to set this up a little bit for what we have here today — will express an opinion that everybody in the courtroom thinks they understand the meaning of. They use terms like "substantial contributing factor," "sufficient to cause," and things like that.

And what you find if you take the opportunity to probe and you are curious enough and skeptical enough to probe, is that an awful lot of experts — and this doesn't apply to the ones we had here today at all — will use terminology that conveys to you one meaning, and they mean something that is really the opposite.

"Substantial contributing factor," which we played with some here today, is one of those terms. I think lawyers, judges, and commentators really have gotten very confused over that concept.

When an expert opinion is given in terms of substantial contributing factor, most believe they are saying there was a causal connection, that the substantial contributing factor actually made some difference.

But, in fact, in a lot of cases, the experts don't mean that at all. What they mean is that the particular exposure caused a risk, a possibility of causation, that they can call it a substantial contributing factor. I strongly suspect that, in these cases, experts have been told by their attorneys that "substantial contributing factor" is a legal term that they can use if they think there was simply a risk or possibility of causation.

I think this happens today because, as Dr. Greenland acknowledged, that particular phrasing isn't something you see in the scientific literature.

So they come in thinking this is a legal term. The lawyers tell me what it means so they can give the opinion.

And what you find, shockingly so many times, is that when you ask them to explain the criteria that enabled them to come to that conclusion and the thought process, it essentially exposes the fact that they're simply saying there is a risk.

And, in fact, I had one expert, when I pressed him on it, who said, "I call something 'a substantial contributing factor' when I cannot say it was a cause."

In these cases you have to be very careful in scrutinizing what the experts are saying and find out what their private dictionary really tells them that these terms mean.

As lawyers, you think we are the ones most suited to being really careful about and sensitive to nuanced language and weasel wording.

But there's an awful tendency for attorneys, when dealing with experts and scientists, to turn off that sort of sensitivity. I think oftentimes they think they understand what the expert is saying and they don't really press.

In my view, a lot of valuable opportunities to clarify what is going on are lost. And a lot of cases are going to the jury when there isn't really enough evidence as a matter of law to support them getting there.

Daubert hearings give you a real opportunity to explore that. And I find that for a number of experts, if you begin to challenge them on things like that, and they think the matter is going to go into a pre-trial motion that might be heard, they will bail on the case rather than suffer the consequence that an informed judge might enter a ruling on the record excluding their testimony.

So they know what's going on. They know the games that are being played, and they do everything they can to avoid that becoming public.

And I think *Daubert* really provides the opportunity to get into that. We tried to get into that a little bit today.

But it comes up principally with "substantially contributing factor" and, more recently, with terminology about something being "sufficient to cause." Some courts have said just saying "substantial contributing factor" is not enough, you have to say it was really sufficient to cause a defendant's exposure.

And it has the meaning that Dr. Greenland gives to it. That's a real statement of causation. The experts play the same game there.

"Sufficient to cause" means somewhere somebody did, actually did, cause it, but I'm not necessarily expressing an opinion about what happened here.

So I think with that I'll let it go.

PROF. IMWINKELRIED: Dr. Toscano.

DR. TOSCANO: I want you to know I was play-acting. I am not in favor of cigarette smoking. I do believe that cigarette smoking is harmful to your health. I do believe that Thalidomide caused those diseases.

THE COURT: Cigars are okay.

DR. TOSCANO: It was very educational for me because I had never testified, let alone in a *Daubert* hearing. And I, in fact, think that this case was very weak; if you want to show a cause in that particular case, it would be very difficult to show. Probably we would agree that it did cause the disease but not necessarily in that specific person.

I still have difficulty with cause and effect in biological systems. For the most part, I agree with Sander, except I do think that mechanisms are important to understand. We can go back to figuring out how to ferret out the disease, because I don't follow the medical school view that we should cure diseases. I think we should try to prevent them. And if we can know more about why things happen or how things are happening, we can interdict earlier on.

So, I thank you all for your attention, and please don't put out there that Bill Toscano favors cigarette smoking.

MR. SMITH: Let me add one comment, if I could, to sort of follow up on something Dr. Greenland said earlier.

There was a period of time fifteen to twenty years ago when a lot of courts thought that only M.D.s could give causation opinions, and might not even get an epidemiologist on the stand in the cases.

But as you begin to explore how M.D.s are trained and what they do for a living, they are not trained to make causal attribution, they are trained to diagnose and then treat.

So, in fact, it's fairly unusual for doctors to even get into the issue of trying to decide how something came about. They want to know: are you sick, what do you have, and how do you treat it.

I have always been under the view — and I think Bert shares it — that the people actually more in a position to testify on those issues are epidemiologists and people like them, in terms of addressing

causal inferences, and maybe a research scientist like Dr. Toscano, who has an appreciation of how things have come about.

I think there's a growing acceptance of that view. But it's a big change from the way things were twenty-five or thirty years ago, when sometimes you could get only an M.D. on the stand, an M.D. who didn't understand epidemiology and who never really dealt with those issues of attribution.

MR. BLACK: I would like to not as much respond but add to a couple of things that Bob has said.

First of all, on what physicians do as compared to scientists like Dr. Greenland or Dr. Toscano: Scientists diagnose diseases. They try to figure out how to treat diseases —

THE COURT: Doctors do.

MR. BLACK: Doctors, yes. Did I misspeak?

But what sometimes you will see argued is that a doctor can do a differential diagnosis of causation. And there are courts that have adopted that mode of thought.

And the idea is that you are supposed to line up all the potential causes that might be in the whole wide world for a particular disease. That could be infinite because for some things you just don't know the cause at all. And then taking a look at the particulars of the individual's case, the plaintiff's case or the patient's case, you are supposed to decide which one of these multiple causes available to you is the one that most likely did it in this case.

While that mode of reasoning may be appropriate in some circumstances to decide what a cause is, it's not a differential diagnosis in the way that doctors do differential diagnosis in their practice.

So that's a misuse of terminology, and I think that creates some problems with the courts. So with that I agree with Bob.

And the other point that Bob made about the *Daubert* hearings being a wonderful opportunity to educate courts. Perhaps you get more informed decisions, not just from the judge but out of the entire process, by taking this opportunity to introduce more information early on in the proceedings. I think that's true.

But the judge for whom David Faigman clerked, Judge Thomas Reavley, shortly after *Daubert* was handed down — I think just like two or three years afterwards — said that, "Never has a case changed the law so little and practice so much." And I think that's a very important insight.

After all, there were judges, before *Daubert*, who were excluding experts who they didn't think were reliable. But that's a lot more common now. There's a more formalized procedure for doing it.

But as to the underlying law that there's some evidentiary requirement for reliability, I don't think that *Daubert* added to that so much as clarified it. So the idea that this has changed practice more than the law I think is an important point, as Bob said.

As to informing courts, in at least two cases that I have been involved with recently, an interesting alternative to *Daubert* has been courts holding Science Day.

"Come in, lawyers, put on witnesses, no cross-examination," more like a classroom, "and tell us your view of how the science is supposed to work in this particular case."

Now, it's actually three times I'm aware of that. Two of those cases were in state courts that don't have *Daubert*, so there wasn't quite the same procedural mechanism in place to consider expert testimony, but one was in federal court.

That's another way of accomplishing the same objective. Some judges have adopted that approach and some might not, but it's another mechanism available to the court.

THE COURT: Let me cut in. That has become somewhat more common, particularly in patent cases where judges are calling for and the parties are occasionally providing tutorials. Just plain and simple. It's an area of inquiry with which the judge is entirely unfamiliar.

Both sides can bring in a person or an expert or put on a presentation to enlighten the judge in this area of knowledge so the judge has some bases to work with.

PROF. IMWINKELRIED: David.

PROF. FAIGMAN: I have a long list, but I would like to try to open it up for the audience as well. So I will hit the highlights and then we can explore some other issues.

First of all, I will agree that there is a fundamental distinction between differential diagnosis and differential etiology.

I have done a little research on the concept of differential etiology, and it seems to be much more a legal concept than a scientific concept. And perhaps Dr. Greenland would disagree with that. But it's very difficult to find any scientific treatment of the problem of systematically looking at possible general causation factors and then reason them down in an individual case to determine whether this particular factor caused a particular illness that is of interest.

And that is something that would be very worthwhile to explore between lawyers and scientists.

Second, the judge said that he would be inclined to admit the expert testimony, which frankly surprised me. If I were a judge, I would exclude. And I don't think that this is that close of a case. But, being an academic, I can't say "so ordered." I would have to write a law review article explaining why.

But just briefly, I would disagree that saying that expert testimony that's proffered is inadmissible necessarily taints the expert. I would agree that if you said that they are not qualified, that might be problematic for the particular witness.

But to say that the science is not sufficient to get in under *Daubert* certainly will taint that expert here and now. That's just a reality.

But that's what *Daubert* is about. *Daubert* sets a threshold standard. It is calling upon judges to be gatekeepers. And as the Judge said, sometimes it is his duty to do just that. But I don't necessarily think that one ought to do the cost/benefit analysis on an expert's career in deciding whether you allow the litigation to go forward.

THE COURT: Let me make it clear. I said you know it's true. I have excluded a number of witnesses and a number of experts, but you take a look and you know what you are doing. And it's an issue. You have to deal with it.

PROF. FAIGMAN: And I have testified as an expert, and I would have been rather chagrined if I had been excluded as not qualified. That hasn't happened yet.

Knock on wood.

The other issue I think is the question that Bert Black raised about the real outliers. And Justice Breyer's extrajudicial comments about the meaning of *Daubert*, *Joiner*,[2] and *Kumho Tire*.[3]

I guess I would prefer to agree with Justice Breyer's written opinion rather than his introduction to the Federal Judicial Center's *Reference Manual*, the second edition.

I don't actually think that that's what *Daubert* was about. I don't think it was about the real outliers.

If you look at the cases where *Daubert* has had an impact or is sort of playing a role — hair identification, bullet lead analysis, Bendectin, and silicone implants — there's a lot of science, and even polygraphs.

[2] General Electric Co. v. Joiner, 522 U.S. 136 (1997).

[3] Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999).

That is within the general core of what looks like science, but it is sometimes called "cargo-cult science" that sort of follows all the patterns of science.

"Cargo-cult science" refers to certain Pacific Islanders who, during World War II, enjoyed the fruits of allied planes landing on their islands. But when the war ended, the planes stopped coming. The Islanders, however, wanted to find some way to get the planes to return. So they started going through the motions to try to get the airplanes to land again. That is, they did everything that they had observed the US military did to get the planes to land — such as waving the planes in. Although they followed all of the seeming rituals of getting planes to land, the planes never returned. Cargo-cult scientists operate similarly. They follow many of the apparent rituals of science. Yet, still, the planes don't land.

And the fact of the matter is there are real consequences. And this raises an issue that Sander got into a little bit, but I think it was implicit in his discussion. If you admit expert testimony in some of these cases, it has real world consequences.

One of the things that is very often left implicit is the cost of making a mistake — of one type or another, whether you make a false positive mistake or a false negative mistake.

Take the Bendectin case as an example. If the litigation is allowed to go forward in the Bendectin case, Merrell Dow Pharmaceuticals takes the drug off the market. If, however, Bendectin does not cause birth defects, then an effective drug will have mistakenly been removed from the market.

At the same time, if you mistakenly exclude that evidence and you don't take the drug off the market, then you have the potential for many, many birth defects.

When you are making decisions under conditions of uncertainty, there are costs of making one or the other type of error. Of course, these are the sorts of judgments that we make all of the time in the law. For example, we adopt different burdens of proof depending upon the consequences that flow from making mistakes.

In criminal contexts, we adopt the beyond a reasonable doubt standard because the old saying is, "It's better to let ten guilty go free than to convict one innocent person." We are simply making a judgment about what the costs of making a mistake are in the criminal context.

Whereas, in the civil context, we adopt the more likely than not standard because we are really agnostic, we're ambivalent, about where we make the mistake. We don't care where we leave it.

Sander's language was apt: where would I put the dollar bet.

Well, implicit in that, I think, and he can certainly respond to this, is some sort of a judgment about where the error should lie in terms of how you spend that dollar, how you put that dollar down.

And that raises just one additional issue that is worth talking about. That issue concerns what is being referred to as the "more likely than not" standard.

I would suggest that the burden of proof on general causation — that is, what it takes to get over summary judgment and get into court — should be a more likely than not standard.

In fact, in many jurisdictions, the expert is actually required to say the magic words, things like "to a reasonable degree of medical certainty" or "to a reasonable degree of scientific certainty." And I don't think that's necessarily the same thing. In fact, I don't think most scientists know what either more likely than not means, reasoning from general causation to specific causation. Remember, that the general causation issue is not the ultimate legal issue.

So to use the ultimate legal standard of more likely than not to stand in for the judgment of when general causation evidence is sufficient — and the word "sufficient" is in Rule 702 — to allow it to get past the general causation problem is sort of mixing apples and oranges.

And we have to sort of step back and say, at what level of confidence about the general proof do we need to allow it to move on to the next stage? But I very much agree with Bob's point, and I think you see this among very sophisticated defense counsel, that they very often target specific causation.

In many cases, the defendant will grant an assumption regarding general causation and just attack the evidence on specific causation grounds. That can be a very effective strategy. In fact, that was the strategy in the Seroquel litigation.

Seroquel is an anti-schizophrenia drug, a schizophrenia treatment that was alleged to have led to diabetes because it induced obesity. The problem is that this was a population that was prone to obesity and diabetes in any case. And in a lot of the litigation, they couldn't prove specific causation and summary judgment was ordered as a consequence.

I think I will end there. I think there are lots of issues that are worth talking about.

PROF. IMWINKELRIED: I agree with what David just said. His comments raised a lot of issues.

So why don't we take one last pass on the panel and then we'll turn to questions from the audience.

Sander.

DR. GREENLAND: You raised this issue about "to a reasonable degree of scientific certainty." And, of course, I've been told, "Well, you need to put this in your report or else it's going to be thrown out and not going to be worth it."

So I have to think about can I say that? How would that translate to my colleagues? Can I defend them? That's my standard of going to work. I presented a case on campus yesterday. There's the Chair of the Department there in the audience. In which department was it?

UNIDENTIFIED SPEAKER: "Population Health and Reproduction."

DR. GREENLAND: And he was there and lots of people.

I presented, and I said here's a case where I can say to a reasonable degree of scientific certainty and have that understood by my colleagues and understand how I could defend being certain.

To me, that's more certain than more likely than not. It is an expression of certainty. It will be much more than just a dollar here and a dollar there.

But that to me should be the test. That's my personal test. Could I present this? Would I publish this in a peer-reviewed journal for my colleagues to see? But I see that so many of my colleagues don't do that. And that would be a question to raise for a judge in a *Daubert* hearing.

"Could you actually defend this before your colleagues in a presentation of a scientific meeting?" And of course I will answer, "yes."

But I saw one solution in two hearings where I was involved. The court had their own experts. And at the *Daubert* hearing, I was asked to defend an expert I really couldn't defend. They really wanted me to defend him. "Could you defend him?"

It got to a certain point where they said, "Can you defend this." The expert was not just an M.D.; he was both an epidemiologist and an M.D.

They said, "Can you defend what he said here?" And I said, "No, I can't."

So he was struck under *Daubert*. But to me it was because of the advice the judge was getting in this hearing from her expert. There was somebody the judge could go to — a neutral expert who could say

whether the plaintiff's expert could defend that in a scientific meeting. Or is he just BS'ing?

MR. BLACK: The reasonable scientific certainty. It's another term which may have some meaning to some people. But as Bob suggests, when language like that is used, explore what it really means to the expert.

I wrote some articles on this twenty-five years ago. There are two cases from Missouri on this topic. It's just fascinating.

This was an automobile accident case. And the issue was whether or not the plaintiff's back injury had been caused by the automobile accident.

And the plaintiff's expert says there's a ninety percent chance that that the back injury was caused by the automobile accident.

Plaintiff's verdict.

It was reversed because the expert had not said there was a reasonable degree of medical certainty. He said ninety percent chance, but it has to be reasonable medical certainty.

So it's reversed. It gets retried.

The expert the second time around (for reasons that are not clear from the opinion this time) says ninety-five percent chance, but also said that that was "reasonable medical certainty."

Again, appealed. It was affirmed this time.

So what difference is there really? The five percent?

UNIDENTIFIED FEMALE SPEAKER: In science there is a huge difference.

MR. BLACK: The five percent difference in what the probability is. The fact that the expert didn't use magic words. Under those circumstances it's just magic words.

Nobody knew what reasonable medical or scientific certainty meant to either the court, the jury, or the expert.

DR. GREENLAND: I can speculate on where the ninety to ninety-five went.

THE COURT: Two standard deviations.

MR. GREENLAND: Because of the five percent significance standard. You have to get to there.

MR. BLACK: That might be it, although if you read those decisions, I suspect that level of sophistication was not present.

Anyway, the point is that you need to understand what the terminology means if somebody is going to use it. It might have some meaning to an expert, but explore what that means.

THE COURT: Let me run down a couple of quick things.

I was interested to ask whether or not he had been examined by the judge.

In a *Daubert* hearing, it's a hearing for the judge. I question a good deal about qualification, and at least I hear my other colleagues do the same. They do a great deal of examination because they want to find out what this person's qualifications are.

Daubert always struck me as really a competency test. Is this person competent to offer this testimony under the Rules 700 series? Will it be helpful to the trier of fact?

The second thing I would like to mention is very important to me as a judge. Scientific causation is not the same as judicial proof. You are not conducting a scientific enterprise in the courtroom. You are conducting a trial. It is a trial tried to lay people.

And the question is how can you get useful information to a layperson from which they can draw a useful conclusion?

Peer-reviewed articles. One of my former law clerks went on to become a law professor. Once that happens, of course, you have lost all control.

But he became interested in junk peer-reviewed articles. And one of our conversations that we had as we were preparing is that there are planted articles so that later you can potentially refer to the articles. And there are bad articles. You have to understand where *Daubert* came from.

Harry Blackmun was counsel to the Mayo Clinic. He worked with the medical and scientific experts at the Mayo Clinic. And that was where he got his ideas — not that I'm saying they planted his ideas — but his ideas were based in part on that experience.

And I think that some of his reliance on peer-reviewed articles came from his work with his colleagues at the clinic who had been dealing with the problems in their articles.

I am not convinced, nor have I ever been, that a judge's obligation in *Daubert* is to decide which side is supposed to win. Nor is it to decide whether or not the proof is conclusive on either side.

It is more, is this opinion within the ambit of those opinions which a competent expert in the field would give? Is that person competent in the field, are they speaking within the area of the expertise in that

field, and would an expert in that field (based on this information) render this opinion?

They always render differing opinions, but that doesn't mean either one would be excluded. And so there's a fine distinction there.

It's not my job to decide in a *Daubert* hearing who is supposed to win the lawsuit. That's a different question, and it gets back to a different way of looking at the question.

I will say one last thing. I was a judge. I sat for twenty-five years. Until today I never heard the genesis of "can you testify to this fact within a reasonable degree of," and then you insert any group you want. This became the flavor of the week. It started somewhere in the late '90s, and then from then on, all the experts testified about was within a reasonable degree of something certainty.

PROF. IMWINKELRIED: That there is an opinion dealing with firearms testimony that was handed down a few years ago in which an expert testified to a reasonable degree of "ballistic" certainty.

THE COURT: You hear it all the time.

PROF. IMWINKELRIED: Bob.

MR. SMITH: Just to comment on the judge's earlier point about experts often cancelling one another out.

Toxic tort cases are my perspective; usually I'm on the defense side. If a matter of toxic tort goes to the jury, we have evidence of negligence on the manufacturer side; they are a bad company; we have people who are injured.

The deck is really stacked against you, if you are the defendant. The chances of getting a defense verdict are slim to none.

In many of these cases, the real challenge is to develop the evidence in advance of trial and try to keep out the plaintiff's evidence. The challenge is to get their experts to concede that they are unable to provide opinions that are admissible under the *Daubert* criteria and that meet the plaintiff's burden of proof.

That's why in these cases I tend to focus an awful lot on the specific causation, what the experts are really saying. I think so often you can show that the experts really do not have opinions that are sufficient to meet their burden of proof. If you can do that at the *Daubert* stage, you can win the case at that point and keep the expert out.

But if it's a battle of the experts when you go to trial, you are really in a hole if you are on the defense side in most of those cases.

MR. BLACK: Defendants do win from time to time.

THE COURT: The plaintiffs will tell you how hard it is because of *Daubert*, and the defendants will tell you the burden is on their side. And the answer is that it's a fight.

DR. TOSCANO: I agree with Sander's comments about what is defensible to your colleagues.

To me, the lingo of the courts assumes a very odd sense of certainty that as a scientist I would not have had.

You say a certain degree of blah-blah-blah. It's hard for us as scientists to say that's true, unless you are certain of the data, the statistics — all this stuff that you would do and could you defend it among your peers.

I think that's a very critical standard. I would like to see that recognized in court, but I guess it will never be that way.

PROF. FAIGMAN: I have just one thing to quickly add — well, maybe a couple of things. Maybe it's good I'm on the defense side here on the table. And hopefully I won't be held in contempt. But I guess as somebody who teaches this, my inclination would be to disagree with the Judge, respectfully, of course.

THE COURT: When they say "respectfully," you are about to get a ram.

PROF. FAIGMAN: I don't think that it's just a competency qualifications evaluation at all. I think that qualifications are a separate requirement under the Federal Rules of Evidence.

And we say *Daubert*, but it's actually Federal Rule of Evidence 702.

And Rule 702 does require the judge to be the gatekeeper to evaluate the underlying methods and principles, and that means an independent assessment.

One point that the Judge made that I would just try to pull apart a little bit is that it's not simply whether the expert is competent within his or her field. There's another question. In fact, Justice Breyer said this explicitly in *Kumho Tire*. It's a question of whether the field is competent as well.

So the judge has to make a judgment about the field. So if you are coming from tea leaf reading, astrology, maybe hair identification, perhaps handwriting identification, and other areas, there's a question of whether the field is itself adequate. And if the expert is perfectly

mainstream in a field that the law should not recognize as competent, then it's the judge's job to step up and say that.

The other point is that I very much agree with the Judge's observation that there is a lot of muddling through. This is certainly my distinct impression.

So much occurs at the preliminary stages — that is, through motions in limine — because juries simply don't understand the basic scientific or statistical issues before them. They don't understand what Sander Greenland is talking about.

I'll give you a concrete example. There's an early decision in a silicone implant case that *The Washington Post* reported on, and it was in favor of the plaintiffs. The reporter interviewed the jurors after the fact, and he said, "Well, you know, the defendant, Dow Chemical, had these incredible experts and yet you found for the plaintiff. Why was that?" And the juror who was interviewed — and I realize that this is merely anecdotal, or what Professor Chris Slobogin likes to call "anecdata" — said, "Well, you know, we as a jury didn't believe the defense expert because they kept looking at the ceiling, they were sweating, and they had beady eyes."

I went to graduate school in science, and, again present company excepted, I haven't met too many good scientists who don't have beady eyes, don't sweat on cross-examination, and don't stare up at the ceiling when they are talking.

Those are not the cues that you should use to evaluate the credibility of expert testimony. It is the quality of the data, and the quality of the methods, that ought to be used. And so jurors are really looking at the wrong things.

And if judges don't step up and understand where the data are coming from, then we will just continue to muddle through as we've done and nothing will change.

PROF. IMWINKELRIED: Let me make one comment before I throw it open for questions from the audience.

We've heard both dissatisfaction from the experts and legal criticism of the practice of requiring the expert to vouch for something to a reasonable degree of scientific, medical, or ballistic certainty.

I've always thought that one of the most important passages in *Daubert* is the clause in which Justice Blackman wrote, "Arguably there are no certainties in science." When he wrote that, he was drawing heavily on the sort of amicus briefs that Bert had filed in the *Daubert* case.

One of the points that Bert made in his 1994 Texas article was that one of the great things about *Daubert* is its frank recognition of the

limits of the scientific enterprise.[4] You can always conceive of another experimental test. And as long as you can do that, in principle you can't accept any proposition as conclusively, absolutely, certainly validated.

It's that spirit that ought to infuse our understanding of epidemiology and this silly practice of requiring experts to vouch for something they can't in honesty vouch for.

Having said that, why don't I just throw it open for questions from the audience. A lot of people told me they wanted to pepper the panel with questions.

UNIDENTIFIED SPEAKER: Professor Faigman, you said that you wouldn't admit the expert testimony. There were two questions, whether Drug A caused the disease and whether Drug A was the substantial contributing factor to this specific person's disease. Would you have excluded both or just one?

PROF. FAIGMAN: From what I saw, once you exclude general causation, that's it. In my opinion, you never reach specific causation if you can't demonstrate general causation. So I will start there.

Yes, I thought it was a very good point that Beta and Gamma had separate patents. You have ingredients A, B, and C in Alpha. A, B, C, D, gives you the independent patent on Beta; and A, B, C, D, E gives you independent patent on Gamma. There's absolutely no basis to say that it's not D or E, especially E because the relative risk was popping up on Gamma.

I found that to be questionable and simply not sufficient.

Clearly there were indications in that direction. I agree that the general causation would be a closer call, but the specific causation wasn't even close.

UNIDENTIFIED SPEAKER: So if it was just the general causation question, if it was the question of going on the Alpha, would you rule for the plaintiff?

PROF. FAIGMAN: Yes, I would have excluded and granted summary judgment on that issue.

[4] *See* Bert Black, Francisco J. Ayala, & Carol Saffran-Brinks, *Science and the Law in the Wake of* Daubert*: A New Search for Scientific Knowledge*, 72 TEX. L. REV. 715 (1994).

MR. BLACK: I think that's far too extreme and contrary to what's happening in other class action cases.

It's generally conceded that statin drugs cause a condition called rhabdomyolysis where muscles dissolve. It occurs at different rates depending on which drug. They are different drugs. They are under different patents. It's a class effect. It's recognized as a class effect.

You don't see much litigation about this now because of the Baycol litigation where the company paid out more than one billion dollars in settlements. After that the warnings are strong.

Consider non-steroidal anti-inflammatory drugs, Motrin and Naproxen come to mind, but there are others as well. They almost all cause stomach bleeds. That was the whole purpose for Vioxx, because it was supposed to be a drug that didn't cause stomach bleeds.

They are different patents. They are a different substance. They act in different ways. But it's a class effect. It's recognized as a class effect.

You don't see lawsuits about their causing stomach bleeds because that's recognized as a risk and people are advised about the risk.

And there are other examples of class effects with drugs even though there are different patents. Some are taken intravenously sometimes and others orally, as an example. Yet they are recognized as the same class of drug, and scientifically it's recognized as a class that causes the condition.

So I do not think that if this case were developed fully, even with what we presented today, there should have been an adverse ruling on the general question.

On specific causation, yes.

PROF. FAIGMAN: I will go quickly because I know Bob wants to speak to the general point. But I think you are going beyond the record to make your argument, Bert.

Based on the data that were provided in this proceeding, I understood that was the question, and on that I don't think there was sufficient basis to support general causation. But I think Bob has a response more to the broader point.

MR. SMITH: I think it's probably obvious to everybody that we tried to construct this so that Bert would handle general causation and I would win on specific.

But I'll play the devil's advocate on this. The fact that there are other situations where a class was recognized for a group of different drugs, that all have the same mode of action and can be lumped together, doesn't mean that's what happened here. In this case, we don't know what the mechanism is. We don't have information indicating that the

thing that makes them polystatols is descriptive of what's going on biologically here.

So I think there are some questions. There are examples where you have group classifications where you can lump everything together. But that doesn't mean you lump everything together where it happens to be described as part of a class when you don't know that the classification can be linked to the causal mechanism.

MR. BLACK: That's true enough. But this is always part of a typical pattern that you see where a drug goes on the market. It's a very popular drug; companies make a lot of money on it. Next another drug company wants to make something to compete, so they develop something that gets around the patent so it is different. It goes on the market. It turns out to cause the same effect. It turns out to be worse for the effect than the first drug.

So the effect is not even recognized until it really starts occurring in large or larger numbers because of this drug that is really bad.

Then they go back and say, wait a minute, now that we look for it, it's showing up in every single drug in this category.

That certainly is true with the statins after Baycol. They go back and look at the statins. Now there's a warning about muscle problems with all the statins because it was recognized. Baycol is off the market. It was the worst. It also was less effective than some of the others. It was a drug that never should have come on the market.

It's also true with the bisphosphonates that are used to treat osteoporosis. Everybody is familiar with Fosamax, Boniva, and the drugs typically taken by osteoporosis patients.

There are much stronger versions of those drugs, so strong that they are given intravenously for cancer patients who suffer much more severe osteoporosis. They cause a condition called osteonecrosis of the jaw where the jaw bone essentially dies. This was not recognized until the really strong version went on the market, and oral surgeons started seeing people showing up with dead jaw bones much more frequently than in the past. In almost every case they were taking a biphosphonate drug.

Sometimes it was Fosamax, and sometimes it was Boniva and some of the others — not as frequently as with the intravenous drugs, but it was there, too.

Now, you have a question under those circumstances. The manufacturer of Fosamax says, "We couldn't have known this was an effect of the class until the much stronger drug caused it." That's a fair argument. "And as soon as that happened and it was a possibility of

our drug, we put a warning on it. And so we shouldn't be held liable with these cases."

That's another argument.

But on the question of general causation when it occurred at a much higher rate with a later drug, you can go back and look at the earlier drug. You implicate the whole class. And that's recognized scientifically.

PROF. FAIGMAN: Let me push on that a little bit. If you recognize that something has general causation but as a practical matter you are not going to be able to prove specific causation in case after case in the tort system, isn't there a public policy social concern once you recognize that reality?

And if that's the case, well beyond the trial process, what do we do as a society? If it's a regulatory matter, you step in because you have population data indicating that the relative risk is going through the ceiling. But if you can't prove specific causation, then you know there's a problem, but nobody's recovering.

MR. BLACK: One of the issues that shows up in evaluating epidemiologic evidence is that you haven't proven general causation unless there's a doubling of the risk. Wrong.

If you have a big enough study that shows that relative risk is 1.5 instead of 2, it is a statistically significant relative risk. 1.5 in repeated multiple studies! The drug is causing some cases.

It may not be more than half of them, so you would have trouble the way the law interprets epidemiologic evidence. Now you would have trouble proving specific causation. You keep the evidence out, but it would be on the specific causation point.

Here, if you recognize the problem because the Gamma drug came on the market and was much worse, that triggered your knowledge about the class. You go back and say, "Look, it's the Alpha drug." You have a patient who is taking the Alpha drug and went blind with this particular disease. The Alpha drug caused it. There's not a problem in proving specific causation there.

There is a problem in those cases, given the way drug companies often react. Some don't react, but that's another issue. The Alpha company might say, "Whoa, that's a possibility for us. Let's preclude liability by putting a strong warning on them that there's been reports."

This case had a specific causation problem because somebody took two drugs. Actually, I don't think this case had a real specific causation problem except for the fact that the Alpha company is in the

case. The Plaintiffs' lawyer who brought this case against both companies would have committed malpractice. Why complicate your case with that and create some doubt about the causation?

THE COURT: But the Beta party would have brought the other one in.

MR. BLACK: It is much better to have Beta or Gamma bring them in than for you to do it. Then let the two drug companies fight over the causation issue and offer proof against each other instead of the plaintiff taking on that burden by pleading it initially.

Although if a case were structured that way, if it got pled that way, I think the plaintiff would still probably be in somewhat the same situation.

Obviously, David and I disagree somewhat.

UNIDENTIFIED SPEAKER: I have a question about the judge's role as a gatekeeper. And I want to preface it by saying that, with due respect to Judge Rosenbaum and present company, most judges were lawyers and most of them were not lawyers in the scientific field. In fact, I've heard it said that the definition of a federal judge is a lawyer who knows a senator.

THE COURT: Or had one for a roommate.

UNIDENTIFIED SPEAKER: My question is, how can we say that most judges have enough scientific training, background, and sophistication that even with Mr. Smith's help (and you try to educate the judges), the judges can make a scientifically valid *Daubert* decision?

I've had jurors, and you talk about lay jurors. My most recent jury had a chemist. I've had engineers, doctors, and nurses. Most judges don't have that background. So how can they render a valid scientific opinion?

THE COURT: Well, you have to back up.

If I had been smart, I would have gotten into medical school; and my mom would finally have been proud of me. But I wasn't pre-med. I had my sciences, but I didn't have the modern electrical stuff because that didn't exist when I was in school.

But the reality is, if you do the sociological studies, and heavens knows they have, you are absolutely correct. Judges studied the liberal arts in college. They were not scientists. And now they are called upon to judge not just science in general, but cutting-edge science.

And how do they do it? They do it like they do everything else. They do the best that they can.

The Federal Judicial Center publishes thick volumes, which each judge steadfastly pores over almost every night. They are edified by programs put on by experts in the field. And they really are. They are recipients of tutorials.

I think that legal briefs, when you learn how to read them, are sources from which judges learn a great deal about both the law and the disciplines that are involved. Then they hear the testimony.

They are about as good as you would expect people who work very hard at making good decisions are. They make some good ones, and they make some bad ones. And I think that's part of the deal.

People in the securities industry are much of a mind that the area that they work in is really so sophisticated that most judges can't handle it. They have actually sort of won because everything is now in arbitration.

And people in the patent field are of a mind that they are dealing with cutting edge information that is not really within the realm of most judges. So it should be in the patent courts. And they have now got a whole circuit that does nothing but that.

People who deal in modern medical technology and cutting edge medical are of a mind that lawyers and particularly judges are not competent to handle those things.

People who are dealing with automobile reconstruction are of a mind that they are dealing in such a specialized area that regular judges can't handle those things.

People who deal with constitutional issues are of a mind that they deal with philosophical issues of such complexity that the average judge is not going to understand them.

And people in the commercial area are of a mind that once you get into business issues, it is so sophisticated that an average judge can't handle it.

And you're right.

UNIDENTIFIED SPEAKER: When the symposium started, you seem to have indicated that following *Daubert*, the number of cases going to trial has been reduced. From what I have heard from the Judge, it sounds more like they ought to let the cases go forward.

So I am not quite certain I'm following why the number of trials is declining.

PROF. IMWINKELRIED: The question relates to whether *Daubert* is causing the decline in the number of cases going to trial, or are judges taking a liberal attitude and letting the cases proceed.

The empirical studies indicate that shortly after *Daubert* there was a discernible increase in the percentage of cases in which summary judgment was granted. But that was a sort of educational period for both the bench and the bar.

The bar then learned that this was a new game, a new test with new terminology. After that, we essentially went back to the prior rate of granting summary judgment.

But I do think that David is absolutely right. If you put all of these things together, it's no accident that we have a system now that promotes pre-trial settlement. Again, the sheer numbers dictate that we've got to encourage that.

In some states, only six-tenths of one percent of the cases go to trial, yet you have burdened court trial calendars. The system has to have incentives built in, procedures that encourage pre-trial disposition.

So that is part of the big picture, but I wouldn't suggest that *Daubert* alone is driving that result.

MR. DEHAAN: By way of introduction, I'm John Dehaan. I'm a criminalist, and I have a few of my colleagues here.

I've been a criminalist for forty-two years. I've testified more than 300 times in twenty-five states and four foreign countries, both civil and criminal cases.

DR. GREENLAND: What is a criminalist, please?

PROF. IMWINKELRIED: John is an expert in arson and explosive analysis.

MR. DEHAAN: The issue is that, as was pointed out by several members of the panel, my career is not in my hands when it comes to a *Daubert* hearing.

I'm counting on counsel to represent me. I'm counting on the judge to make appropriate decisions.

My question is, how do I make sure that the person putting me on is properly prepared to represent my interest as an expert and make sure I don't get slammed?

I've been the target — I'm sorry, subject — of four *Daubert* challenges in the last ten years or so. I just had one of them quoted to me in a national seminar about how bad my judgment was, which is pretty embarrassing.

But I didn't get a chance to respond. There was no debate. There was no cross-examination or rebuttal. That was in the hands of the U.S. Attorney.

So how can I make sure that the person putting me forward as an expert is going to fairly represent my science?

PROF. IMWINKELRIED: The question came from John Dehaan.

John's point was that his reputation really is on the line when there is a *Daubert* challenge. How can he make sure that the attorney putting him on is going to present his testimony in a way that his reputation will be protected?

Before I put this question up for other comments, let me just say on more than one occasion since *Daubert*, I have told experts, "You tell that attorney that unless he or she invests the time to learn the science so that your reputation will be protected, you tell them 'I'm not taking the stand.'"

There are times when the attorney is acting so irresponsibly that you have to rub their nose bluntly in the fact, "It's not just you and your client, it's me as well. And if you are not going to invest enough time that I am confident that you will protect my reputation, I'm not going to be your witness." I think sometimes that's warranted.

PROF. FAIGMAN: I'm happy to also speak to it.

I think you do have a slight advantage. Even though you are a criminalist, you don't testify on the side of the criminals. You are usually on the state side or the government side.

But I very much agree with Ed's point. I have testified in a number of cases (in forensic evidence cases, in fact). Public defenders who have very big dockets might fly me in, and I do it mostly on a pro bono basis. But when I sit down, I might have only an hour to talk with them about how I am going to testify.

Now, luckily, in both *Frye* and *Daubert* hearings, it does tend to be fairly informal, and so the judge will either sort of take it over and ask questions or allow me to explain my answers.

I think once you get to the trier of fact or the jury, it ends up being much more formalized, and you have to rely on your attorney to be paying attention and to be up to speed.

But I will just add one other thing: I do a lot of judicial education, and judges always say two things to me after we speak.

The first thing they say is, "Do you have a checklist that you can give me so that I can use this?" They all want checklists. And it would be great to come up with something sophisticated enough that they could rely on.

The second thing they say to me is, "Tell the lawyers I don't really have the power to object. I can't really initiate a line of questions."

I actually see *Daubert* moving from an adversarial process to a more inquisitorial process. Most judges are uncomfortable in that role, and most judges will say, "You are not going to get really effective representation in our adversarial system unless you also provide that checklist to the lawyers too."

And remember, all judges are former lawyers, and I teach these now budding lawyers. And I can tell you when I put a normal distribution on the board or I try to calculate a standard deviation, my students either run from the room or their eyes glaze over. They don't want to have anything to do with it.

If you got straight A's in Russian literature at UC Davis, the best advice you can get is to go to law school. Those are the people that are trying the cases, and those are the people who know senators and become judges.

UNIDENTIFIED SPEAKER: Speaking of criminalists, in 2009, the National Academy of Sciences issued a broad ranging report relying largely on *Daubert* to conclude that although a number of areas of forensic evidence analysis had previously been so well established they were virtually unassailable, most of those areas of analysis are just scientifically invalid and unreliable.

What are the implications of that, and where do you think that's going to lead?

PROF. IMWINKELRIED: The question is the impact of the 2009 NRC report, *Strengthening Forensic Science in the United States, the Path Forward*.

That report has had an important effect. You see it cited widely. And it's raised the consciousness of the limits of some of these forensic disciplines.

It's not the only thing that's contributed to it. *Daubert* itself and *Kumho* contributed to it.

You see some real changes. For example, you see limitations now on the phrasing of the ultimate opinion.

Not in 2009, but a few weeks ago, the National Institute of Science and Technology released a new report on fingerprint examination.[5] And one of the things the NIST says is, "We don't want to hear fingerprint examiners saying any longer, 'I can identify that person to

[5] NAT'L INST. SCI. & TECH., LATENT PRINT EXAMINATION AND HUMAN FACTORS: IMPROVING THE PRACTICE THROUGH A SYSTEMS APPROACH (2012).

the exclusion of every other human being on the face of the earth who is now alive, who has ever been alive or who will ever live.'"

The report dovetails with that line in *Daubert*, "arguably there are no certainties in science."

The other thing you see occasionally is the use of cautionary instructions. For example, consider the first major case applying *Daubert* to forensic science, the 1995 *Starzecpyzel* decision involving questioned document examination.[6] At the end of that opinion, Judge McKenna phrased a cautionary instruction saying in effect, "I want to tell you that these people aren't scientists. They are more like the tugboat pilots who have enough experience to edge the ship into the dock without destroying it. When you go back into the deliberation room, consider the fact that they aren't full-fledged scientists."

The combination of these reports and decisions about *Daubert* really are having an impact. And there are even more important impacts long-term. You see this in questioned document examination and fingerprinting. It's created an incentive to do the research that many of these forensic disciplines should have done 50 years ago.

PROF. FAIGMAN: I would agree with that. I think that one of the biggest benefits of *Daubert* is that fields that had not been traditionally rigorous started going out and doing the research.

In fact, if you go look at questioned document examination, if you look for studies prior to 1993, you are really hard-pressed to find anything. Post-1993, there are about a dozen pretty decent studies. Moshe Kam, in particular, has conducted several respectable studies that have begun to move the field in the right direction.

And I think that if, to be quite frank, federal judges started excluding or limiting forensic evidence, the field would mature much faster.

If judges stepped up and said, "Until you produce the data, we are going to limit what you can say about this evidence," the Justice Department would immediately start spending a lot more money than they are spending now.

The NIJ actually is stepping up and starting to spend money, but nothing like what the National Science Foundation spends every year and not even close to what the National Institutes of Health spend every year.

And I would echo Ed's point. First of all, I don't think the NRC reports said that these sciences are invalid or these statements or

[6] United States v. Starzecpyzel, 880 F. Supp. 1027 (S.D.N.Y. 1995).

opinions are invalid; what they were saying is that there are insufficient data to say what they say in court. It simply has not been studied adequately yet.

But I do think when you go back — and Ed's been publishing on scientific evidence before me — we started writing our treatise in 1993-94. The first couple of items came out in 1997, but we, Michael Saks in particular, were screaming about forensic scientists coming in saying we had a zero percent error rate and that we never make a mistake.

That was standard fare. The custom is changing. There are a number of criminalists in this room whom I know. We are learning to trust and start developing partnerships because the scientists who know statistics and how to design research methods don't necessarily know what the fields know about cartridge cases, bullets, or other things that you might want to study.

And so the real trick here — and it's going to take money — is to bring the criminalists together with the methodologists and start designing research that can produce good quality data.

And as Sander said when we were talking during the break, one study or a couple of studies really don't prove anything. You need to get a corpus, a real volume of research, to support the kind of expert opinion that's being offered day in and day out in courtrooms.

UNIDENTIFIED FEMALE SPEAKER: It was interesting to me to hear the professor say that he would have excluded this testimony today because what I heard was a lot of statistics and methodology.

I work in the trenches in criminal defense, and so I find myself dealing with handwriting experts, gunshot residue, hair, and gang experts.

My impression, or maybe just my own paranoia, is that there is a different gatekeeper for a criminal than there is for civil. At least the *Daubert* standard appears to be different.

And I was wondering if the panel can comment on that. Your last comment seemed to be that there needs to be this corpus behind some of these fields, and it's not there. But we're still getting the testimony admitted.

PROFESSOR FAIGMAN: The question, and it's a great question, is whether *Daubert* is being applied consistently on the civil side and on the criminal side.

One of my colleagues, Michael Risinger, a professor at Seton Hall, published an article in the *Albany Law Review* where he systematically looked at that question.

The conclusion that Risinger reached, and a number of people have reached, is exactly the one that you suggest. And that is that courts are much more rigorous about admissibility standards on the civil side, especially when it came to plaintiffs. I think Bert might agree with this. That judges in civil cases were taking their gatekeeping role quite seriously, and that a lot of plaintiffs' experts were being excluded because *Daubert* was being applied rigorously.

On the criminal side, in contrast, it appeared that a lot of forensic sciences like hair identification and some others had very weak support, and in other cases virtually no support, but were being admitted.

Hence, *Daubert* was being applied rigorously to exclude weak plaintiff expert testimony in civil cases, but was being applied permissively to permit weak prosecutorial forensic evidence in criminal cases.

Latent fingerprints is a good example of this duplicity. There are very few studies out there that demonstrate that they can do what they say they do.

Now, again it's conceptually appealing, but there's a lot that hasn't been demonstrated. Questioned document examination is really just kind of a black hole. But the judges were letting it in. Prosecutors never met a judge who applied *Daubert* rigorously. Why that is, one could imagine.

One possibility is that a lot of judges are former prosecutors. They were proffering it when they were attorneys. Therefore, they know it, and they have come to trust it.

Also, they majored in Russian literature or history, and they didn't know it was a problem. And it's just now being pointed out.

Also, defense counsel weren't raising objections. In fact, public defenders have taken a long time to get up to speed on raising objections and really challenging this kind of evidence. So the dynamic just wasn't occurring.

I think that's changing. The NRC report will give some ammunition to public defenders. I certainly get invited to do more public defender talks than D.A. talks, at least. But I've been invited to do D.A. talks and U.S. Attorney talks as well. So I think it's just taking time.

I do see Judge Reavley, whom I clerked for, and I think it's a telling quote. But I actually think that *Daubert* is a revolution of sorts. You don't measure revolutions in a decade or two.

I think that we won't really know what *Daubert* wrought in terms of increasing the sophistication of the legal community for sometime yet.

I now teach a Scientific Methods for Lawyers class. There are all sorts of initiatives to bring more education to judges and to lawyers.

That was a consequence of *Daubert*. *Daubert* basically says to lawyers and judges, welcome to the twenty-first century. A great thing about being a judge is that you are a generalist, but being a generalist today means that you have to understand regression analysis. You have to understand what random match probability is. You need to understand basic concepts of biology if you are going to preside over a DNA profiling case.

THE COURT: Gang experts and drug experts would testify all the time. One of the things I did certainly did not warm the hearts of the United States Attorney's office. The standard practice was that either the investigating agent or police officer was also allowed to testify as an expert about drug notes and the meaning of words that they used and the way drugs are distributed. You cannot possibly be an expert in your own case. But that's very common, as you are quite well aware.

But you are absolutely correct. The number of objections from defense counsel is very small.

Set aside fingerprint and certain parts of hair analysis, which has now gotten a little better because of DNA. Ballistic evidence is pretty slippery stuff. There's all kinds of good data. However, you have to be careful because all these knives have two edges. Much better data could make it admissible.

Be careful what you ask for, because you might get it.

MR. BLACK: It's somewhat the question of resources and just what people's habits are in the criminal area versus on the civil side.

Four or five years after *Daubert*, I was participating in a panel — like this one — at the Texas Bar Association's annual meeting. Judge Hitner, I think, was serving in Judge Rosenbaum's role. Since I'm working for a defense law firm at this time, I'm on Bob Smith's side at that point.

And there was another defense lawyer sitting next to me saying, "Yeah, all my clients demand that there be a *Daubert* motion in every case. If we don't file a *Daubert* motion in the case, we're going to hear about it from our clients."

But if it's not merited, why are you doing this? I was getting ready to say something, and the judge says, "You're going to get Rule 11 in my court if you do that."

The idea of doing it frivolously because your clients want it is just not acceptable.

But I think that on the defense side, clients expect it, and the lawyers learn how to do it as a routine part of defending the case. But I don't think that's so on the criminal side.

I haven't defended criminal cases, so I don't know from personal experience.

I will relate one other anecdote, because it just shows the extent to which the defense lawyers will routinely file a *Daubert* motion.

And this involved —

THE COURT: This is on the civil side.

MR. BLACK: This is on the civil side, yes.

This involves a construction litigation case about a garage that was falling down. I have as my expert Mr. Garage Designer for the United States — well, certainly for the upper Midwest. If there is a garage engineer association, he's won prizes for them and done stuff for the state of Minnesota. He designed and supervised the construction of the big garage at the Minneapolis-St. Paul Airport, if anyone is familiar with that. This guy knows his garages. Right?

Not only did he know his garages, but he was familiar with this building in particular. It was an older building. It had been an apartment building that was converted to a condominium, and he had worked for the prior owner when it was an apartment building.

In Minneapolis, apparently because garages sometimes collapsed due to all the salt and everything used in the wintertime, there's an ordinance that the safety of every garage has to be inspected and certified every year by an engineer. And he had been the inspector for this garage before it had been converted for condos.

This guy knew the garage. He was an expert.

It's not a *Daubert* motion, but the defense lawyer invokes the state court equivalent in Minnesota to exclude his testimony because that's what defense lawyers do with experts. You are going to file a motion to exclude. And that's what the clients expect.

And this wasn't a defense lawyer who was an S.O.B. He was the kind of guy you liked practicing against. And his whole point was, "Well, he's going to be prejudiced because he's going to be grading his own work from when he did the inspections."

That's an interesting thing to raise about weight and credibility. But under *Daubert*, the question is whether the methodology is wrong. He doesn't know what he's going to be testifying about. He was allowed to testify, and the case went forward.

The fact that a motion to exclude was filed under those circumstances shows how deeply ingrained this is becoming in defense practice.

PROF. IMWINKELRIED: Let me just say one more thing in response to your question. I think it's a great question.

I had a long conversation about this with my friend David Kaye at Penn State several years ago. Not by way of justification but by way of factual explanation, David thought that the phenomenon, the differential treatment of forensic science in criminal cases and plaintiff's testimony in civil cases, reflects of the continuing importance of the general acceptance factor in *Daubert*.

We may no longer have *Frye*, but general acceptance is still one of the factors. In the minds of many judges, it is perhaps the most important factor.

Prosecutors tend to rely on traditional forensic techniques while plaintiffs often resort to novel causation theories. David's speculation was that that may be the single most important explanation other than bias for this differential treatment.

UNIDENTIFIED FEMALE SPEAKER: So it's like the tea leaf readers. If you ask a whole lot of tea leaf readers, it's all good.

MR. BLACK: And it's the lack of resources by the criminal defense bar to bring the kind of challenges that you see on the civil defense side.

UNIDENTIFIED SPEAKER: Going back to the point you just made as far as relying upon credibility of the experts within their own field.

The thing I have observed here is that both of the experts would rather that be the sole criterion, going back to *Kelly-Frye*, looking at the general acceptance in our field.

It seems to me that the point, though, is that *Daubert* places the burden on the judge to put the entire field on trial. It really gives him the tools to take it away from just the general field of practitioners and to take it upon himself to be the judge of a field. I guess that it's more of an observation than a question.

DR. GREENLAND: I want to make a comment.

That's the one that I have the hardest time with because everybody will come in and say yes, this is generally accepted. But the reality is that that may mean only that the colleagues whom I work with accept it. They may represent some small minority of the field. The expert who testifies to general acceptance may even believe it's true, but that's selection bias because he talks to a few people and dismisses the rest. It may be the general field regards what they are doing as witchcraft, more or less.

Sometimes the field just seems to be suffering from semi-permanent splits.

For example, the last big split involved the statistical methods surrounding significance testing and hypothesis testing. Some of you may know already that there are people like my co-author Rothman who regard testing as witchcraft, and then there are the other extremes of people who regard testing as an absolute must for any scientific credibility.

That split has been there for sixty or seventy years among accepted leaders in the field.

So what's generally accepted, if one testifies to that? And the answer is, nothing is generally accepted here. It represents a highly controversial field.

PROF. IMWINKELRIED: And claims of general acceptance are often made at such a high level of generality that it's almost meaningless.

Years ago, one of David Faigman's co-authors, Professor Saks, sent out a questionnaire to questioned document examiners.[7] The questions were about particular techniques and particular assumptions in their field.

He found tremendous divergence among equally credentialed, equally experienced QD examiners.

They would all testify that, generally speaking, handwriting identification is generally accepted. But when it came down to nuts and bolts — the specific methods and techniques — there was tremendous disagreement.

UNIDENTIFIED SPEAKER: This is a related question. Are you, any of you, aware whether or not the trends of future dangerousness are being subjected to the admissibility issue?

THE COURT: Future dangerousness?

UNIDENTIFIED SPEAKER: In criminal sentencing.

PROF. IMWINKELRIED: The question relates to, are there any new trends with respect to the treatment of testimony about future dangerousness.

[7] Michael J. Saks & Holly VanderHaar, *On the "General Acceptance" of Handwriting Identification Principles,* 50 J. FORENSIC SCI. 119 (2005).

PROF. FAIGMAN: I actually write on the subject. The short answer is no. And the reason why is rather complicated. Just to step back for a moment. Predictions of violence are relevant everywhere in the law: pre-trial detentions, before trial for juveniles, parole, probation, capital sentencing, ordinary civil commitments, and civil commitments of sexually violent predators. So psychiatrists and psychologists are regularly asked to make statements about the likelihood that someone will be violent in the future.

First of all, the law begins with the assumption that the factual issue is relevant and somebody must have an answer to it. Therefore, we are going to go out and find the expert who is willing at $500 or $1,000 an hour to provide an answer, regardless of whether there are data that might support it.

In this area, I studied with John Monahan at Virginia. He's one of the gurus in this area, and he's developed actuarial tests that are used.

What is fascinating is that this is an area that is actually growing and developing on using actuarial tests to predict violence. Yet when you go out and look at what courts are doing on a case-by-case basis, they will not allow the actuarial tests to come in by themselves. In addition to the actuarial or statistical test, they require a clinical judgment to be offered even if there is no reason to believe that the clinical judgment is reliable or valid in any general sense.

In fact, Paul Meehl, a well-known psychologist at the University of Minnesota who passed away some years ago, was famous for his study comparing statistical predictions versus clinical judgments. He found that statistical predictions invariably were better than clinical judgments.

There is even research suggesting that when you add clinical judgments to statistical predictions, they get worse. They actually go down. Yet courts continue to rely on it.

And it gets even worse than that. Even when they consider the predictions of violence, they don't really evaluate the underlying foundation for the test. They don't even investigate what the threshold should be for what is sufficient to deny somebody their liberty and incarcerate them because they are mentally ill, mentally abnormal, or a sexually violent predator.

Just to illustrate this — and this will make the scientists' brains explode — in a very famous case, *Barefoot v. Estelle*, a capital sentencing case, the U.S. Supreme Court considered the constitutionality of Texas' requirement that the State prove that the

defendant is likely to be violent.[8] This empirical proof was an aggravating factor under the Texas death penalty statute.

The issue was whether the admission of expert predictions of violence violated due process given the fact that both the American Psychiatric Association and the American Psychological Association concluded that they cannot predict violence in any reliable fashion. In fact, they stated in a brief to the Court that they are wrong two out of three times.

Justice White wrote that although the associations say that they cannot predict violence and that they are wrong two out of three times, they are not wrong all of the time. He actually said it. Therefore, the Court concluded, it was not unconstitutional to use reliable (and invalid) predictions of violence as a basis for a death sentence.

In that case, Dr. Grigson, who is known as Dr. Death in Texas, testified that he was 100 percent certain that the defendant in that case would kill again if he were not executed.

PROF. IMWINKELRIED: But just remember one point about the legal context. If you are talking about sentencing, ordinarily *Daubert* doesn't apply. You are dealing with a due process standard of admissibility rather than the *Daubert* standard.

PROF. FAIGMAN: That's true. But even in the civil commitment cases where the rules of evidence do apply, they don't do a *Daubert* analysis.

And one of the reasons for that may be that the substantive law requires a psychiatric or psychological assessment, and that, arguably, the requirement trumps the procedural evidentiary requirements.

UNIDENTIFIED FEMALE SPEAKER: Am I not correct that *Daubert* is a federal rule and that not all states apply *Daubert*? I don't think California does.

[8] *Barefoot v. Estelle*, 463 U.S. 880 (1983).

PROF. IMWINKELRIED: Right. The majority of states now have adopted a variation of *Daubert*. There are still fifteen states, including California, that formally adhere to *Frye*. But the caveat is those states include California, Florida, Illinois, New York, Pennsylvania, Washington. These states are both large and litigious. Thus, even though you can say that as a formal matter, only a minority of states still adhere to *Frye*, it may still be true that the majority the state trials are governed by *Frye* even today.

UNIDENTIFIED FEMALE SPEAKER: But I was wondering has there been any study? Is there a difference that you can see in the result of those that apply *Daubert* and places that have not?

MR. BLACK: The answer is yes. There were some articles published maybe ten years ago. I don't know what's happened since then.

But this is anecdotal. I don't have any evidence on it. Maybe David has done a study.

I think that the inclination to examine expert testimony closely has penetrated the non-*Daubert* states just as much as it has the states that have adopted *Daubert*.

Your testimony is more likely to be challenged now no matter what state you're in than it was before *Daubert*. Minnesota doesn't have *Daubert*, and I just told you that story about the defense lawyer who is going to automatically challenge every expert.

PROF. IMWINKELRIED: You may be familiar with the Lockheed Litigation case in California.

That case ultimately was dismissed by the California Supreme Court because so many of the justices had stock in relevant companies. So many of them had to be recused that they couldn't get a majority to decide the case.

Having said that, the intermediate appellate court analysis in that case was very similar to a *Daubert*-style analysis, proving Bert's point about *Daubert* penetrating even *Frye* states.

David and I submitted an amicus brief in that case urging the court under 802 of the California Evidence Code to formally adopt that position.[9] That same issue is now pending before the court in a case involving the University of Southern California.[10]

[9] *See* Edward J. Imwinkelried & David A. Faigman, *Evidence Code Section 802: The Neglected Key to Rationalizing the California Law of Expert Testimony*, 42 LOYOLA L. REV. L.A. 427 (2009).

[10] In November 2012 after the date of this symposium, the California Supreme

So sometime in the middle of this year we may get a better inkling of how far *Daubert* has penetrated California.

UNIDENTIFIED SPEAKER: One more question. I deal mainly in state court, so I am not super familiar with *Daubert*. But on the standard of review on appeal after a *Daubert* hearing, what happens at that point? I'm sure you stick to the record and all that. But it seems as if it has to be *de novo*. It has to be something that you can't just rehash with just three more judges.

PROFESSOR FAIGMAN: The question is, what is the standard of review on appeal?

The doctrinal answer to the question comes from *Joiner*, the Supreme Court's 1997 decision. In *Joiner*, the Supreme Court articulated the abuse of discretion standard, not the *de novo* standard.

What is interesting in the argument, and I mentioned it this morning, is the problem with applying the abuse of discretion standard, which is the ordinary evidentiary standard for preliminary facts.

When a trial court is deciding whether there was enough excitement for an excited utterance, or whether statements were made in furtherance of a conspiracy in order to meet the exception for co-conspirator statement, those are all factual questions that the judge is to decide. The judge can assess the demeanor of the individual to decide whether the particular legal rule applies.

When you talk about scientific evidence such as the question whether polygraphs are valid because you're looking at heart rate, blood pressure, and sweating on the skin, that's a general question. The issue is whether the physiological reaction demonstrates deception, whether PCR is a valid technology for DNA profiling, or whether second-hand smoke causes lung cancer. Those are questions that transcend individual disputes.

It strikes me — and I think it strikes a number of federal judges — that *Joiner* was incorrect in saying that the appellate court should be deferential on the general causation scientific questions. You could imagine two cases, for example, that involve handwriting expertise.

Court decided *Sargon*. 2012 Cal. LEXIS 10713 (Cal. Sup. Ct. Nov. 26, 2012). Although the court did not wholeheartedly embrace *Daubert*, the *Sargon* decision moves California much closer to the federal approach to determining the admissibility of expert testimony. David L. Faigman & Edward J. Imwinkelried, *Wading into the* Daubert *Tide:* Sargon Enterprises, Inc. v. University of Southern California, *2012 Cal.LEXIS 10713 (Cal.Sup.Ct. Nov. 26, 2012)*, 64 HASTINGS L.J. (forthcoming 2013).

One is tried in San Francisco and the other in Oakland. If one court allows the evidence and the other excludes it, should the appellate court — the Ninth Circuit — be deferential to both on the question whether handwriting expertise is sufficiently valid to allow as a general matter? It seems odd, to say the least, that the question of whether a defendant has to confront prosecutor-sponsored forensic evidence should depend on whether he is prosecuted in San Francisco or Oakland.

There is a good example of that. When the so-called implant litigation was really on fire, there were two major locations where the cases were being litigated. One was Sam Pointer's court in Montgomery, Alabama, and the other was Robert Jones' court in Portland, Oregon.

Both judges appointed expert panels to help them judge the general causation issue. Judge Jones' panel, which was appointed by himself, concluded unanimously that there was not sufficient evidence to conclude that silicone implants caused atypical connective tissue disorder. But at this time, Judge Pointer's panel had not yet reported their findings.

Judge Jones wrote an opinion excluding the evidence, but he did not sign the opinion. And he said basically that "I am inclined to follow my panel's recommendation, but I'm going to wait before I finalize this until I see Judge Pointer's panel's report." In short, Judge Jones wanted to be sure to avoid the possibility that a *New York Times*' article would read that women in Montgomery, Alabama, can sue in silicone implant cases but that women in Portland, Oregon, could not.

It would have been perceived as fundamentally unfair if different judges had come to different conclusions based on exactly the same scientific evidence. Inconsistency in results in different courtrooms involving the same scientific questions would create a sense of unfairness.

Actually, a number of *Frye* jurisdictions adopt a *de novo* standard for general scientific issues. Oregon does, and Texas does as well. These are a couple of jurisdictions that I know of that have state supreme court rulings holding that *de novo* review applies to the general principles of science that might be litigated in the cases in those states.

UNIDENTIFIED SPEAKER: First, let me say that I'm a forensic scientist, but I am one who happens to believe that both *Daubert* has had positive effects of the quality of science that's being done, so I am totally supportive.

At the same time, I'm struck here in this proceeding by the fact that what we have here, if you skip to the bottom line on the scientific

testimony, is two different opinions that oppose one another. They disagree with one another. On the face of it, that would seem to suggest that the issue here is not settled in the scientific community.

This debate is between two scientists about how we should regard this, and the judge ultimately said, if I understood him correctly, "I'm going to give it to the jury and let them decide what weight they want to put on it."

I'm wondering about the philosophical intent of this movement. Do we improve science by taking scientific decisions out of the hands of scientists and putting them in the hands of the lawyers? That doesn't seem quite right.

THE COURT: Far be it for me to guess what Harry Blackmun was thinking when he wrote that opinion. However, I think what he was doing was reacting to a felt belief in the legal community that there was bad science being promulgated and pushed around in the courts. Tocqueville said that in this country, all issues wind up in courts.

When they wind up in courts, lawyers get involved. Scientists do not like being pushed around in the courtroom. They have changed their own means of promulgating their own information and obtaining it. They have improved or changed at least their methodology probably to react to a very important legal development.

Scientists traditionally did what scientists do and didn't care much about what happened in courtrooms until scientific proof became more important in cases. At that point the synergy developed that you have described. And I think you are correct about it.

I described another one of the things that has developed, which is junk peer review. You want peer review, I'll give you peer review.

But it's the epistemological problem: the observer changes that which they have observed.

DR. GREENLAND: There are junk peer reviews. Some of you may know, there are all these junk journals now that are published.

THE COURT: Not necessarily JAMA, by the way. The word "necessarily" belongs in that sentence.

DR. GREENLAND: There are now many, many legitimate online journals, but there is this phenomenon. There's also been an explosion of online journals with impressive sounding names.

THE COURT: There are fellows of those institutions?

DR. GREENLAND: Some are located overseas, and they send out peer review and so forth. Basically, if you pay the money, you get published and therefore satisfy the peer review criterion in *Daubert*. They won't be able to challenge that.

PROF. IMWINKELRIED: Our time is up. I would just like to say this in closing.

I also don't know what was in Harry Blackmun's mind when he wrote *Daubert*. But in my heart of hearts I would like to think that one of his hopes was that by using this new standard, we would form a better collaboration and a better partnership between law and science, a more honest and more open collaboration.

I think today we've seen a wonderful collaboration between a judge, attorneys, experts, and an academic commentator producing a wonderful symposium. Thanks to all of our participants.