**THE NATIONAL ACADEMIES**

**SCIENCE, TECHNOLOGY, AND LAW PROGRAM**

# JOINT DISCUSSION OF SCIENCE, TECHNOLOGY, AND LAW PANEL AND AMERICAN LAW INSTITUTE

## RESTATEMENT OF TORTS

**Tuesday, January 21, 2003**

**The National Academies**
**Lecture Room**
**2101 Constitution Avenue, NW**
**Washington, DC**

**Proceedings By:**

**CASET Associates, Ltd.**
**10201 Lee Highway, Suite 160**

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P R O C E E D I N G S (9:00 am)

**Agenda Item: Welcome and Opening Remarks - Richard A. Merrill, Co-Chair, Science, Technology, and Law Program, Daniel Caplin Professor of Law, University of Virginia Law School**

PROF. MERRILL: Good morning and welcome. We've got a lot of really smart and dedicated people who are involved in the exercise. So, we have some considerable confidence that it will prove fun for the participants, we hope useful for the American Law Institute, and the two reporters on the part of the restatement of torts that are responsible for authoring the paper that is under discussion today.

The panel I want to just say a word about, was established just over three years ago, I guess you could say in partial response to the Supreme Court's decision in Daubert, which was surely a signal that the scientific community was going to find its activities intersecting with the legal system more frequently than in the past.

And the Academy managers made a decision that the creation of a vehicle for identifying issues that deserved attention and carrying out projects for which there was interest was a desirable thing to have. And accordingly, they appointed a panel of about a dozen lawyers and a dozen very distinguished scientists.

We've undertaken a number of public projects involving recent legislation -- the Shelby amendment, the Data Quality Act -- that impinge upon the use or access of the public to scientific information in the possession of the federal government. And we have just embarked on, through a new committee that we are responsible for overseeing, but not managing, a study for the Environmental Protection Agency on the use of human studies of non-therapeutic chemicals in regulatory and environmental decision-making.

And if there is anyone interested in what we do, and what we contemplate doing, I would be happy during the breaks or after the session to provide help. Anne-Marie Mazza, who is our panel director, will be more than happy to send you material and information, even donation envelopes. As a former dean, you can't resist that last opportunity.

Let me just say a word or two before introducing my co-host, Lance Liebman, a little about the genesis of today's project. Mike Green, who teaches law at Wake

Forest, and is one of the two authors of the paper under discussion today, called me about six or seven months ago, and said we are working on this project, the restatement of torts. The restatement is going to deal with the question of causation of injury and illness.

We have included in the draft materials, some reporters' notes on what we understood to be the underlying science that would support or illuminate decisions about causation.

But when we ventilated this draft at the last meeting of the American Law Institute in May of last year, we got a lot of questions from the floor, from people who said in essence, how do you know your science is right? And he asked, is there any way that the Academy or the panel of which I was co-chair, could help address that question?

The NAS procedures for addressing questions of any sort are, it is fair to say, complicated, slow, and expensive. Very often I like to think the end result is worth the time and expense, but it was quite clear that the usual procedures of the Academy for the production of a report by an appointed expert panel were simply not practical in this circumstance. Time didn't allow it. Resources weren't there to do it.

And so, we have tried to fashion a novel procedure, I think, that we hope will be of assistance to Bill Powers and Mike Green as authors of the reporters' notes on the restatement to the American Law Institute and its members in their deliberations next May, and not incidently to the ongoing work of the panel, of which I am the co-chair along with Don Kennedy. I'll have a little bit more to say about that procedure, and how we got to where we are in just a minute.

But first, I would like to introduce as co-host for today's event, Lance Liebman, who is director of the American Law Institute, and the Beinecke Professor of Law at Columbia, and I am proud to say, the former dean of my law school.

Lance.

**Agenda Item: Welcome and Opening Remarks - Lance Liebman, Director, The American Law Institute, William S. Beinecke Professor of Law, Columbia University**

PROF. LIEBMAN: Dick, thank you very much.

Let me just say a couple of words about the American Law Institute, even though those of you who are not

from the law side of this meeting received this in a written form. As with my students, I know you have read the whole thing and are fully prepared.

But standing here, it does occur to me that the American Law Institute was founded in 1923, with goals not unlike those of the very eminent organization whose building we are sitting in. Here was an attempt to get together, people in law -- judges, professors, and practicing lawyers -- in a private organization to give advice, and to give it essentially to courts, but also sometimes to Congress and state legislatures, to others in the legal system based on their expert and serious thinking about what the law should be.

The other people, the judges and the others, have democratic legitimacy, and they frequently reject what we suggest, but there is some value to our doing this work. So, I think it's a perfect occasion, given as Dick just said, the interconnections of the scientific issues with the legal system and its work, a perfect occasion for these two organizations, Dick's committee and our reporters, to come together, and to speak together, and see if we can help each other.

Let me just say a couple of other things. Mike Traynor, who is there, is the president of the American Law Institute, and made a 24 hour round trip from San Francisco in order to be here today, which if we had a group to give him advice, we would have advised against it, but he did.

And two members of our governing council, Ken Abraham from Charlottesville, and Bill Wagner, who has been waiting a long time for Tampa Bay to be in the Super Bowl, and finally got there.

Let me be the one who makes the apology. For all of you who struggled through this document, and it would be a difficult, important, challenging piece of reading even if it were clean, I apologize. I didn't do it, but I apologize for the fact that in the interchange between Word and WordPerfect, and whatever, you got a thing which duplicates some paragraphs and some sentences, and shows you where they changed some words, but it left the old words in it put in new ones. So you've got to be real smart. We wouldn't want you here if you weren't smart, so you can handle it.

The other thing I would say -- well, let me say two other things very quickly. One is I want to say to those of you who are the non-lawyers that I'm very confident

that what you are reading in this draft is quite a good summary of the state of the law. So, if your initial reaction is, this is stupid, nd what country would go about deciding multi-hundred million dollar matters and doing things that lead to changes in research and other behavior, what country would do it this way, I just want you to start from the idea that this rough, imperfect, logically questionable, et cetera, regime that is decided here is approximately where the law is right now.

We hope and believe, because we all have faith, and that's why we participate, that the country can do it better, and that the legal system can do it better. And that's what we hope to advance in this meeting. But, you ought to know that.

The second thing is I was struck reading it, not for the first time yesterday -- not even for the first time in the last week or something -- but I was struck reading it again that there are a number of important matters about the way the legal system deals with these kinds of disputes that are not addressed right here.

And they are matters that the American Law Institute is addressing in other parts of this project, and projects we haven't started yet, and things we have done before, et cetera. And they include -- and to me it kind of leaps off the page -- they include the question of what the standard of responsibility is.

In other words, this proceeds basically thinking about a negligence regime, and that's not necessarily a given, but it's a given in our system. And there are issues about that, that are not part of today's discussion.

And then all the questions involved in class actions. In other words, what happens when there are 100 or 1,000 or 30,000 more injured or ill people? What kind of regime do you come up with? Much of the discussion in this document, it seems to me, rather assumes that there is an individual human being with a claim. And of course, the system becomes much more complicated and imperfect when it is seeking to do justice for a large number of people. That's a subject where the American Law Institute hopes to be doing work in the future.

The final thing, which I'm sure you'll hear over and over again is we're here to participate, to talk, to communicate. And that doesn't have to end today. And we hope everyone in the room, in all of the parts of this room

will feel free to contact me, Bill Powers, Mike Green, to let this conversation go on as you have more thoughts, and as today's discussion gives rise to more thinking later.

But I'm just delighted that this meeting has finally come to be, and I think we will all benefit from it a great deal.

**Agenda Item: Discussion of ALI's Reporters' Draft - Moderator: Richard A. Merrill**

PROF. MERRILL: Thank you, Lance. I and we, the Academy's panel really share that optimism and enthusiasm.

Just a little bit of background about the process for today. I won't regale you with the amount of time and effort we spent as members of the panel, in identifying potential candidates among the scientific community for serving on this panel this morning. We started with a roster of distinguished epidemiologists and scientists in relevant fields of about 120, and through internal evaluation and discussion and consultation with many other parts of the Academy, arrived at a shorter list.

Our qualifications were eminence, interest and experience, and willingness to commit the time involved to this exercise, including the preparation for being here today. We invited about nine or ten, and the gentlemen that you see before you are those who were available on the schedule that we had to meet.

And without further ado, let me just briefly introduce them. I bill them as the lions for today's event. And I'm delighted to see Dr. Steve Goodman has weathered the traffic and the weather to get here. Steve Goodman is associate professor of oncology, urology, pediatrics, epidemiology, and biostatistics at Johns Hopkins. Are there any other faculty?

DR. GOODMAN: That's an example of the Web interface gone berserk. Not everyone is ranked, but most of them are.

PROF. MERRILL: Leon Gordis is professor of epidemiology and director of the Johns Hopkins Robert Wood Johnson Clinical Scholars Program. Jerry Kassirer is distinguished professor and assistant to the dean at Tufts University School of Medicine, and senior research scientist at Yale School of Medicine.

David Savitz is chair of the epidemiology department at the University of North Carolina in Chapel

Hill. And Doug Weed is chief of the Office of Preventive Oncology, and dean of education and training in the Division of Cancer Prevention at the National Cancer Institute.

Now, playing the role of Christians are our two reporters, Mike Green, who is a professor of law at Wake Forest Law School, and Bill Powers, who is professor of law and dean at the University of Texas Law School, both eminent scholars in the field of torts and injury law. And it is their work product that is the subject of discussion today.

In terms of what we hope to deliver physically, first is a transcript of today's meeting, and the memories, recollections, and notes that Bill and Mike carry away from today's discussion.

I know Mike will repeat this, but I will say it too, we would be delighted, but we are not seeking to impose any obligation on any member of the science panel, if individuals might wish on reflection, to assemble their thoughts or notes, or add something to a comment today by way of letter to Bill or Mike. I know they would be grateful, and we would applaud that.

The written transcript will be made available to them and to the institute as well, and it will be a public document. Will it be on our Web site eventually? We will cross that bridge, but it is not going to be a private document. It is open for exploration and deliberation by members of the institute when the work product of our reporters comes back to the institute.

Now, just a final word about the many observers who are in the room today. We are very glad you could come. We hope it's a satisfying and interesting day for you. And if there is time available in the schedule, we will provide an opportunity near the end of the day for you to make comments and ask questions of the scientists. I'll try to keep a list of people who are interested in making a statement, or asking some questions near the conclusion of today's discussion.

But we want to afford maximum opportunity for the reporters and the scientists to interact during the course of the day. If that opportunity is fully exhausted, and there is still time on the calendar, we will make it available for anybody in the room. We will invite your participation at that time.

Now, my job is, I think, to get out of the way so that the conversation between Mike and Bill and their

scientific colleagues can proceed. I think Mike and I have reached a tentative agreement, I hope it still holds, that you will kick off, and engage the conversation. And we hope it flows without any intervention from the host or the chairs.

PROF. GREEN: Bill and I view our role here as primarily listening, rather than talking. But there are a few things that we would like to state up front. First of all, we would like to thank each of you for taking the time out of your schedules to read this document, and come up here and spend this time with us. We really do appreciate that, and we are quite confident it will benefit us significantly. We're not sure what the benefit is for you, but we're pretty sure we are going to get a lot out of it.

As you probably know, for some 30 years now at least, courts have been confronted with a number of cases that involve disease and the question of whether some agent is responsible for that disease. And there has been a significant body of law that has developed over that period of time, punctuated in I guess it was 1993 with the Daubert decision that regulates the admissibility of expert witnesses. But it's not just in federal courts that this has happened. State courts have also conducted these kinds of cases.

This document that you see is an effort consistent with what the American Law Institute has done over the years to gather this case law, to try and synthesize and summarize it, and to make a sensible statement about it that can go to judges. It is primarily addressed to judges who might get cases like this, but also lawyers who are involved in these cases, with the most sensible synthesis of the law that has developed on this subject.

As you may have been able to tell, one of the things that we have carved out, and that we are not addressing in here is the question of the admissibility of an expert witness' testimony. A lot of law has developed in that area. For a variety of reasons, we believe that's not within the scope of what we are trying to do.

So, we are really addressing the question that arises if the testimony is admissible, what evidence is sufficient? And that gets to an important question that overlays tort law here, that is implicit in this document, but not explicit. And that is of course a critical question in all these cases is who is going to ultimately decide the

case? Will it be the judge, or will it be the jury?

There are two ways in which judges decide cases. One is the admissibility of evidence. If evidence is not admissible, one party may lose, because they simply have no evidence on a critical issue. And then other question is, even when evidence is admissible, is it sufficient to permit a jury to make the findings that a jury has to make? In this case, it would be causation.

So, what we are addressing here is the question of scientific evidence and its sufficiency. To permit a jury, or, on the other hand, for a judge to say, no, this is not sufficient to make a determination of causation.

A couple of other constraints. Unlike science and boxing -- you may wonder what science and boxing have in common -- in law no-decisions are not possible. Cases are decided, and that decision is final, at least for the parties who are involved in that case.

The second is that cases are adjudicated based on individuals, and not on groups. Unlike, for example, the regulatory context where we might be interested in increased group risk, the cases that we are dealing with in this document are about individuals, and whether an individual's disease was caused by the agent that was identified.

Lance already apologized, but I would like to say that he's right, he didn't do it. But the state of that document, and the repeated words is the result of the tenacity of the author/reviewer mode in WordPerfect. If anybody can figure out how to turn it off once it's been turned on, I would like to know.

Combined with the translation of WordPerfect to Word, which is not entirely smooth. And that's why we try and keep track of changes we make. Unfortunately, that keeping track resulted in the garbage that you see in this document, and I apologize for that.

What we do have to accomplish today? Well, I think our view is that we are here to listen to you. We are here to hear you about the science that is in this document, and how it might be improved, modified. If you want to praise us for the rest of the session, that's fine. We'll sit here and listen.

You may also want to critique the law that has developed. I think that will be less helpful for us. We are not going to persuade courts that they should stop using relative risks and odd ratios to make individual assessments

of probabilities. We may be able to better explain the conditions that are necessary for that, and why one should be cautious in doing that. But that's well established in the jurisprudence of today in these cases, and it's not, in all likelihood, going to change during our lifetimes.

So, with that, we are here to listen on any subjects that you want to raise that are in here. We have specific subjects we will raise at the end if there is time, but our view is we want to hear what you have to say.

Now, let me start out by saying that the framework that you see in this document -- like we do in law school, we'll start with the Socratic method. The overall framework in this document is to identify three critical subjects -- exposure, the idea of general causation, or whether an agent is capable of causing in the human species the disease in question, and maybe we should qualify that, at the doses that humans are exposed. And then finally, this question that is necessary because of the way we do it of specific causation.

Does that make sense? What are your reactions to that?

DR. GOODMAN: Can I throw a question back to you? This is based on a very extensive body of writing in this area already. It would help me if I had a better sense of what is exactly the role that you were trying to -- you already stated it, but many people have outlined some of these things already it seems. Or maybe they haven't, and you can tell us that.

So, what did you find most difficult about synthesizing that body of evidence? And to what extent does this differ in some ways from other accepted summaries of these key concepts?

PROF. GREEN: You're absolutely right, this is not original, and doesn't purport to be original in any sense. But this is a document that, when it's completed, and it's finally approved, will come out with the endorsement -- well, it will be an American Law Institute document. This is not a document that will say authored by Mike Green and Bill Powers. It will be an institute document.

Since it was created in 1923, the institute has spoken authoritatively and influentially to judges about what the law is. And so, the purpose, the reason for this is not an individual author's statement about his or her views about this matter, but rather, an institution that has

a significant amount of credibility among judges in being objective, and being intelligent about trying to pull together diverse strands of law.

So, that is both purpose and what it is, why this document is what it is. I'm not sure if that's entirely responsive.

DR. GOODMAN: That is to the first half. The second half would be what were the diverging bodies of opinion that you found most difficult to sort of synthesize or reconcile that you think would be potentially lightning rods in this synthesis?

PROF. GREEN: Now I'm reflecting on this draft has been around for a couple of years, and it's gone through several meetings of the institute in which it has been commented on and discussed. I think one of the major issues that has arisen has been the question of whether there is a threshold relative risk that should be employed for adequate proof of causation in an individual.

Does there have to be a relative risk of slightly greater than 2 in order to translate? You all understand the connection between a relative risk of 2 and a preponderance of the evidence standard? Okay. That has been a significant lightening rod that we have had a fair amount of discussion, and revised this a number of times in light of that discussion.

What else has been?

PROF. POWERS: To the lawyers, this is a controversial topic, because it is a screen through which a case has to go to get to a jury to be decided, if it's going to be decided, to be decided in favor of a plaintiff. And this is an issue that plaintiffs' lawyers are much less fond of than defense lawyers.

So, one of the issues has been how much of this to do, how much should the institute get involved in restating the scientific underpinnings of what courts have done in this area. That's not a specific answer to the question, but it's been very controversial in just how much, and in what kind of detail, and what kind of specificity this should be laid out.

Which led to the notion that what is laid out ought to be sound from the scientific point of view, and not just clerks' references to their views of science that might be underpinning a quite controversial doctrine.

DR. GOODMAN: What are they most worried about?

PROF. POWERS: Well, I think for example -- this is from the plaintiff's point of view -- when you start granulating a doctrine, for example, there must be evidence of exposure, then general causation, then specific causation. That clerks will granulate their analysis of the facts, and say we don't have anybody testifying on general causation for example. Or the expert on general causation doesn't qualify under Daubert.

Now, we are not addressing the admissibility question itself, but if for example, the expert on general causation is disqualified on Daubert, and then there is no evidence of that particular granulated aspect of the analysis, then the case does not have enough evidence to go to the jury. As opposed to just the standard is but for the defendant's conduct, the injury would not have occurred, and then have the science just part of the jury argument and the credibility.

DR. GOODMAN: So, the very issue of how you have laid out the components of the scientific argument is a big issue for many of the potential consumers of this document?

PROF. POWERS: I believe so.

DR. KASSIRER: I find this pretty scary, not because I'm facing 40 lawyers, but because I'm sandwiched between four epidemiologists. The last time I was among so many epidemiologists was when I was at the New England Journal of Medicine, and then they were all from the Harvard School of Public Health. You can understand how scary that could be.

I view this as an extremely ambitious and difficult task. Viewed from the standpoint of a clinician that I guess has thought about causality for a long time, and written about causality not from an epidemiologic standpoint. It seems to me that to try to draft a document that would satisfy both sides of an argument, the plaintiff on one side, and the defendant on the other, is really tough to do, because you can be sure that if the plaintiff's side likes it, the defense side won't, and the other way around.

And to try to walk that fine line in the middle, I think is difficult. And part of the difficulty it seems to me to be the consequence of a difference in the way that the law and medicine views information. In medicine, information is kind of cumulative. That is, a study is done which supplants a previous study, or two or three studies are done which then permit a new analysis of a problem, and

the new analysis then becomes the standard.

Which is quite different from the way the law works. Now, I'm preaching to the converted in the sense that the way the law works is to take a case, and once a case is decided, then the case becomes the standard. So, there is a difference between how evidence is used or information I guess is used in medicine versus the way it's used in the law.

You made the point that in law, no-decision is impossible. You can't have no-decision. But I think that's certainly true of medicine too. One-on-one dealing with a patient, it is certainly true that no-decision is a decision. That is, a decision to operate or not, to treat or not to treat, either way, it's a decision that will influence the clinical course of a patient.

And finally, I just throw this out, a quote from a previous paper that Joe Cecil and I wrote which is, "Unfortunately no set formula or algorithm exists for deciding whether a human illness or condition is the consequence of a given exposure to a drug, chemical, or some other agent." There is no set formula, and ultimately the decision is one of judgment. So, I'll start off with that.

DR. SAVITZ: It's not a bad idea. As I was talking in contrasting -- and from experience in part as an expert witness -- but trying to sort of translate how it differs from my day job. In other words, how it differs from being a researcher, and someone who evaluates evidence, and so on in that arena.

And besides the general issue of working for a degree of conclusiveness, as scientists we try to absorb all the information. And in absorbing all the information, in many cases it leads us to varying shades of gray. It's not black and white. And obviously, in making these judgments, it does need to become black and white for the legal purposes.

But I think another part that is unfamiliar, at least to epidemiologists, and this may be an interesting difference of actually clinicians who do deal with individual patients ultimately, and must make judgments, we get uncomfortable I think typically in going from the general causation to the specific causation.

I live in the land of the general causation. I may not always have the answers, but I know how that arena, what the issues are and how that operates. So, then I've

gotten to the point now where I can describe what I think we know based on epidemiologic studies of groups who have this kind of exposure, what magnitude of increased risk they have, et cetera.

And then it comes to the question, and did it contribute to this patient's illness, this person's disease? And there is a feeling in epidemiology now, and maybe it's informed speculation, and that is maybe what is needed there, but I'm always trying, well, maybe if I break a large group down into smaller and more refined groups, so I can actually use the information.

It's not just he's a smoker. He's 20 years smoking two packs a day. Now, I've got him in a little cell. And then get to a point, maybe eventually we'll have it to the point where we know his genetic make-up or whatever. But trying to make it less of a dichotomy between the general and the specific. I want to keep moving along a continuum there, because it feels like a leap otherwise. Maybe it is a leap otherwise, to make that step.

PROF. GREEN: I just would observe on that, David, you don't find it in this document, because of the way this document is structured and its audience. But certainly, if one were writing a monograph on epidemiology and the law, or actually in the federal judicial center, a reference manual on epidemiology, it makes explicit what you just said.

That when you get to specific causation, this is not epidemiology or something that epidemiologists, in their day jobs, think they are doing. This is something that the law has done with the output of epidemiologists, because again, of the constraint of individualism.

I think we make that point in here, maybe in too subdued a way that one should understand that this specific causation idea is not one that epidemiologists do. Sometimes they do when they are doing their consulting jobs, of course. But it's not something that one would see, or that they would attempt.

DR. SAVITZ: Also I would say, conversely, again, I have seen cases where a clinician is quite comfortable in saying, this is my patient. I know why he or she got what he or she got. At one level it's either a different scientific process or bad epidemiology sometimes. And it really is very hard.

I'm in no way intending to be critical of clinicians as a group, but sort of in that setting, with

that question posed, there often is the willingness to take that leap, and to say I know about this person and the influence on them. And to someone building a case of course, and I understand the sort of structure, you want all those pieces to be in place.

PROF. GREEN: I guess what would be helpful to us is given that we are in a world in which this is being done, the need to explain the assumptions, and the qualifications in doing it, that we should be clear about in the process. For example, that an association that is found is not necessarily causal. Don't translate from relative risk to probability. Those are the sorts of things that I think this document can contribute to people who are using it, who are not inculcated in the sciences that are involved.

DR. GORDIS: In terms of the overall document, let me say that I had a basic feeling of being on the same wavelength, but it's probably because I had the pleasure of co-authoring a chapter in the reference manual with Mike. So, I think we have discussed a lot of these issues over time.

The point that he just made though about the issue the specific causation not being part of epidemiology I think is much clearly stated in the reference manual chapter, which I brought along to read to you. And what the section says:

"Epidemiology has its limits at the point where an inference is made that the relationship between an agent and a disease is causal where the magnitude of excess risk attributed to the agent has been determined. That is, epidemiology addresses whether an agent can cause a disease, not whether an agent did cause a specific plaintiff's disease."

And then it goes on in terms of talking about this relative risk issue. "The question is not a question that is addressed by epidemiology, rather it is a legal question that the upper courts have grappled with. And the remainder of this section should be understood as an explanation of judicial opinions, not of the epidemiology."

Well, I think the chapter draws a very clear distinction. So, I'm still not clear on what our role is, if we still agree with that, in terms of discussing this specific causation piece here today. We're not commenting, I see on the judicial process for whether the courts are making appropriate decisions. Are we just talking about it

from the scientist's standpoint. And I think that was reasonably well decided.

I would also like to mention that I think, Mike mentioning you can't have a no-decision situation. And several of my colleagues here have already spoken to this. The fact that the issue of uncertainty is part and parcel of science. Today's truth may be refuted tomorrow. And we are not used to, in our scientific or academic culture, to reaching a definitive, immutable statement.

In fact the old joke that goes around, we should state that further studies are needed, because there are always further studies needed when we finish our seminars. I always tell my students, you say it sitting here in the Johns Hopkins seminar room, but for the person at the front lines, and I usually don't refer to lawyers, but so much of the health officers, policymakers, and so on, you can't just say further studies.

You might get those studies, but you've got to make a decision today. And if the decision is not to regulate, that's as much a policy decision as a decision to regulate. So, I think the luxury of delay is something that academics have, that may not exist in a courtroom or in the policy arena, and it's an important distinction.

And the last piece I want to mention is that I think that as scientists who deal in the legal arena, it's not a comfortable arena for many of us. And I think even if it doesn't get explicitly discussed in this document, I think it's an important thing to understand in terms of what underlies it.

For example, over the years I have gotten very accustomed to colleagues disagreeing with my findings, or criticizing my studies. But that is very different from the impeachment of the witness. They don't ask me at the same time, how much I'm earning a year, for example. That's not considered relevant. They can disagree on a scientific basis.

And I think it's very important thing. So, many people who really give a deposition or have gone to court, feel very uncomfortable that their "integrity" is be imputed as individuals, and motivation is being brought into the context. And it becomes a very uncomfortable situation for many scientists, and I think it accounts a lot for their lack of enthusiasm about participating in the legal process.

And the other part of this is that the legal

process basically encourages polarization of opinions. With plaintiff and defendant, which side are you on? And I know when I have gotten called, I know that the lawyer, if he doesn't like what I'm willing to say, he'll just go on down the list until he finds somebody who is going to give a good, strong, extreme opinion on one side or the other.

And that's very different from the nature of science, that attempts to develop a consensus based on discussion of what we know, what further studies are needed. So, I think there is a major cultural gap. And over the years, and Mike and I have talked about this in the past, I think there is a need to talk about what can be done to bridge the gap.

And while it's not the purpose of this session, I understand that, but I think it underlies a lot of things even in asking scientists to comment. But it's not crystal clear to me whether you are asking us to comment on the science per se, regardless of who is asking the question, whether it's lawyers or anyone else.

Or you're asking us to really get involved in commenting, which may be a little bold for scientists, to comment on whether you are making the right use of it in the judicial process, and whether the courts are doing the right thing. That's still a little ambiguous to me at this stage of the morning.

PROF. GREEN: Let's start with your comments about science. There are a number of statements about science that are in here. They talk about the use of group studies, and what they mean, and the different kinds. There are statements in here about the use of differential diagnosis or differential etiology.

Mentioned in here, and I think there is some controversy about this, that typically an agent is responsible for a single disease or a group of biologically related diseases. And the fact that an agent causes lung cancer, doesn't mean that it causes testicular cancer, for example.

Those are statement of science, I think, that we have drawn, that the courts have been confronted with in these cases. And that's where we would like to focus at least most of the discussion and your time today.

We can talk about -- and this is partly responsive to your inquiry, what else has raised issues. The question when we don't have the evidence available, when there isn't

good epidemiology, what is sufficient? When should we, nevertheless, permit a judgment to be made?

And of course, there are different contexts in which that arises. It may be that there is no epidemiology for good reasons. It may that there is a body that is accumulating over time, and courts become aware of that. It may that be that exposures are so infrequent that there never will be epidemiology, and we are faced with a very, very small situation that we'll never know; not very definitively. So, I think it's hard to generalize about that question, but that is a problem that we have seen an awful lot of.

Those are the sorts of things that I think we would like to hear your views about during the course of today.

DR. KASSIRER: There is a language problem here that concerns me, in which you imply more certainty in the causal relationship than you are justified in doing so. For example, on page 4, at the top you say, "This in turn means that the plaintiff was exposed to the substance. The substance is capable of causing disease, general causation, and that in fact cause the plaintiff's disease, specific causation." That implies certainty.

And then on page 7, the fifth line from the top, you talk about group study identifying a genuine causal relationship. That implies to me more certainty than you are justified in using, unless you are using it in the sense of the court. The court will say okay, X caused Y. In which case you are justified in saying at least that's what the court said. But from the standpoint of science, I don't think you are justified in saying that.

PROF. POWERS: I have a question for Leon, but I think Doug wants to say something.

DR. WEED: Let me just start off by thanking you for inviting me to be here, and calling me an expert. I was feeling good about that. It reminds me of a story that Yogi Bera, who was always known for his creative use of the English language, when he became the general manager of the Yankees in 1964, someone asked him, do you think you have enough expertise to do this. He thought about it for a minute and he said, "You can observe an awful lot by watching."

And that's a little bit how I feel. I think I may be the only member on this panel who, over the 25 years of

my career in epidemiology, has spent nearly all of my research time thinking about the problem of general causation, among other things.

I have never dealt with the legal issues period. I've never done expert witness work. I can, even at the National Cancer Institute, but I never have. So, I really come to this, and I'm fascinated to be here, with never really having thought about this very much, but interested in thinking about it and having spent, as I mentioned, and writing about the problem of general causation in some considerable detail.

So, if we could, at least from my perspective, move at least in part to talk about what is general causation from an epidemiologic perspective, how do we go about that. I would agree with my fellow panel members, the question of specific causation as a part of our professional activity would be pretty unusual.

I've never really tried to think about it except in a medical context, having been trained as a physician myself. Sure, if someone gets a disease in my family, and my uncle for example, died of leukemia, and he was a farmer, was it pesticide exposure that could have been the cause of his leukemia? Well, maybe so. But that's a different kind of problem than the kind of problem that you have in which you are trying to assign responsibility.

But when it comes to general causation, that's what we are all about. And if we could spend a little bit of time sort of talking about the context of general causation within which there is all sorts of interesting things to talk about within epidemiology.

And it occurs to me again that your concerns about specific causation, or perhaps your decisions about specific causation do rely, in many causes, upon a decision about general causation. Is that correct? Okay.

So, we could at least spend a little bit of time talking about what is general causation, and how do epidemiologists both go about that in their practice. What are the methods, and you have talked a little bit about them, the criteria that we use to make those sorts of judgments.

That would be a very interesting place to start, it seems to me. In fact, interesting enough, the methods, the Austin-Bradford-Hills criteria -- let me just make one very interesting observation about the methodology within

the practice of epidemiology.

If I were to write a review paper today, or join a group looking at the question of general causation, and they were to ask me or this group, so, what method are you going to use? We could say, well, we'll use the Austin-Bradford-Hill criteria. Now, an interesting observation about that is that they were published in 1965. That was one year after the surgeon general's smoking and cancer report came out in 1964, establishing a relationship between those criteria.

It has been fascinating to me that in 2002, an epidemiologist would say let's use a method that was written about in 1965. The fascinating thing about that is I don't know of any other example in the methodology of epidemiology in which we would say it's just peachy to use a 37 year old methodology.

The issue being here is that it looks to me as if the methodology basically been stagnant for 37 years. But that, in and of itself, is an interesting statement, and sort of something worthy of examination and consideration. Why is it that that methodology has, for all practical purposes, not changed in 37 years?

Part of that is that in the training of epidemiology, that methodology has not been a primary focus. We talk a little bit about it. There has not been much research done on the methodology. When I say, that is in contrast to let's say logistic regression, or any form of quantitative -- meta-analysis is another example that is fairly new.

There is a huge effort in research on the methods themselves. And for whatever reason, this methodology, which is largely qualitative with quantitative input, has basically been sort of stagnant for 37 years.

Another interesting feature to this methodology, and when you ask me, well, how do you know what you're talking about, we have actually the practice of causal inference in epidemiology, looking at the way in which we, as epidemiologists, use this method to make claims about causation.

The method appears to be one in which there is a considerable amount of whether we want to call it subjectivity, personal preference. And it comes at a variety of levels. That is, the level of which of the criteria do you want to use? There are nine according Hill.

There were five according to the surgeon general, although those five could be expanded out to give us nine without too much trouble.

You can use pretty much the criteria you want to use. And not only that, you can -- we all define them in a similar sort of way, what they refer to. But the rule of evidence, or the rule of inference that we attach to each one of these can vary considerably by individual user. Let me give you an example, one that you talked about with magnitude of relative risk.

So, what relative risk means causation? Some people say well, if it's under two, then I'm not going to think about it. And other people say, why would that be? Why not 1.7? Why not 2.4? What's so magical about the number 2? And my humble opinion about this is that a 2 is just about as arbitrary as a P of 0.5. It's a convention, something that we accept.

I do not believe that 2 has a strong theoretical foundation for it. In fact, I would argue that there is no theoretical foundation for those criteria, not in a theory of cause leading to those criteria. These are a set of conditions and beliefs. I don't want you to feel like I didn't think Hill knew what he was talking about. Obviously, he was a brilliant man. These have maintained their facility over the years, because they make a whole lot of sense.

But there is this incredibly large amount of individual variability in the use of these criteria of which you use, what are the rules of inference that you assign to them, and what's the priority. Which ones are more important than others?

Now, I can tell you that in practice, at least in cancer epidemiology, which is a big chunk of the practice that I am a part of, the big four are consistency, strength of association, biological mechanism, and dose response at biologic gradient. Those are the ones that we say that we are using.

There is this little guy temporality that we don't actually use as much as you think we do, and there is a reason for that, that we can get into, and I don't want to steal all the time here, because there is so much to talk about.

But those would be the four that you would find most commonly used, given that there is no experimental

evidence. That is, that there prevention trial. That's what Hill meant by experiment. And that's some prevention trial. And that changes things remarkably as the beta carotene in the smokers showed, ATBC trial and the carrot in which the trial basically put aside all the epidemiology that had been published to date.

But given that there is no experiment, and those are the four major -- major meaning those are the ones that are used most commonly. So, I don't want to keep going on and on. Steve may want to say something too.

Just to give you a sense of where I think our field is with regard to the question of general causation, in fact we always make decisions. We either say it's causal, and I would agree with you Jerry, that things can get reviewed, but I don't think anybody on this panel would say that no, I don't think smoking causes lung cancer. I think we do agree to that.

But we have to decide, is it causal, or is it something else that is not causal? It might be causal, but we're not sure. We can't make that claim. And then the other two decisions we have are should we do something about it, or should we not do something about it? I'll just take a break there.

DR. GOODMAN: I'll make two comments. One, I will make the more important one first. I think, and this is in some ways dovetailing directly on what Doug was saying. I think what this is missing, and maybe it's not what should be in this document, but it's certainly the area that I have been involved in some legal proceedings on general and specific claims.

And invariably, the place where I am asked to provide the most input is on issues of uncertainty, both statistical uncertainty, and what I'll call epistemic uncertainty, which is I think related to many of the points that Doug is talking about.

And this handles some of what I'll call the epistemic uncertainty decently well. Uncertainty about the methodology, uncertainty about the combinability relative to various evidence, and many of the dimensions that Doug was talking about.

But it doesn't sort of tackle uncertainty head on, and sort of outline all the contributors for uncertainty, and how we balance and weigh them. And one thing that is glaringly missing I do think is statistical uncertainty.

That exists almost nowhere in this document.

For example, you take as a paradigmatic example, a situation where you state -- I think this relates to what Leon was saying is in the document here -- you state sort of causal facts in this document. The main uncertainty you explore, or issues related to uncertainty about which agent was responsible, or how you apportion blame, and how you might come to different decisions depending on which agent was -- whether they were synergistic or whether they weren't, things like that.

But what is absent from this sort of series of examples, I would like to see this either added or a richer series, is a situation which is the real life situation of course, where we don't know these things. Or we are uncertain to both a partially quantifiable and partially unquantifiable extent about every element.

So, for example, what happens if we just take a very simple example, if you have a situation where you have an observed relative risk of 2.3, and you have a confidence interval, to use statistical language, that goes from 1.05 to 4. And that, by the way, is always the minimum uncertainty. Then you have all these other levels of uncertainty that are layered onto it.

How do you compare that situation to a situation where you have an odds ratio of 1.7, with a confidence interval of 1.6-1.8, with this other uncertainty? And what happens whether that is generated from very great, high quality studies, or a sort of motley collection of studies? And when we know the underlying mechanism, when we don't know the underlying mechanism.

This, in my experience, which is much paler than either of yours, are the kinds of things that scientists actually have to talk about, or it's almost the only thing I'm going to talk about. And yet, how that is brought into play here, it's sort of invisible, some of these dimensions. They all get sort of rolled into we're a little bit unsure.

And yet, this is the one part of the process, at least some of the statistical stuff, is where we actually have numbers. The only number you focused on here, or was mentioned was really that point estimate above or below two. But there is another quantifiable dimension of uncertainty. And then we have this less quantifiable dimension of uncertainty.

So, it seems to me that what this lacks, but

again, this isn't the document to explore it, is a more systematic analysis of what it means to be scientifically uncertain about causality. And it has both the quantitative and non-quantitative components. And I think it has dimensions of most everything that has been spoken about around the table.

And these all go to general causation questions. Everybody will agree here that it's one level more difficult to go to the specific causation. But if the general causation uncertainty issue is not well analyzed, then it seems to me that it's hopeless when you get the level of specific causation.

I'll stop there.

PROF. GREEN: When you say the quantitative and non-quantitative, I just want to make sure I understand, Steve. On the quantitative you are talking about looking sampling error, and the devices that are available to address sampling error?

DR. GOODMAN: Yes. I would say sampling error, and to some extent -- now, this is where we really get into a philosophic debate -- the extent to which you want to quantify some of what the epistemic certainty/uncertainty in quantitative terms. That is, if we are talking about Bayesian methodology, do you want to capture some of that uncertainty -- I never think we can capture it all, but do you want to represent it in quantitative ways?

So, the primary and in a sense hardest form of a quantitative uncertainty is exactly what you said, the sampling error. Sort of the second level, quantitating our uncertainty about qualitative things is to embody them in mathematical representations of what we'll call expert opinion or opinion about biases. And then there is a sort of a third level of uncertainty, which really shouldn't be tried to be capturable in quantitative measure at all.

But, you are right, the primary one and least controversial one is the first part, is the sampling error part. And even that particular part, I didn't really see here.

PROF. GREEN: And again, to make sure I understand, the main quantifiable, and maybe just qualitative are concerns about bias and confounders?

DR. GOODMAN: Yes. They are partially quantifiable.

DR. KASSIRER: I think Steve's point is very well

taken. There is a lack of notion of quantifying associations, which certainly could be added. But one of the problems I think we haven't addressed relative to general causation is the much more difficult and problematic situation in which we don't have quantifiable evidence at all.

And then I think we are in a much more muddy situation. And I would be interested in what my epidemiologic colleagues think they can do about that.

DR. WEED: Let me take a little stab at talking about this. One thing, I think talking about the manuscript itself, a topic that I think would be worthy of consideration is the whole issue of biological mechanism, which comes back to some of the comments you made. Because the way I like to think about that, and it is a very critical part of general causation, and I would argue over the last 25-35 years, it has become increasingly so, as our biologic knowledge has increased.

Biological mechanism is not typically something that you get from epidemiologic studies. Now, with the marriage of molecular science and epidemiology, and molecular epidemiology, that will in fact change over time as well. But traditionally, biologic mechanism is something thatcomes from evidence that is not what you would call epidemiologic evidence. It's evidence from cell lines. It's animal model studies. There are a variety of possibilities there.

But the interesting feature about that in the context of general causation is that there are no criteria for causation in biological mechanisms. Not only are there none from an epidemiologic perspective, I'm not aware that there are any within biology itself. And it is possible, partly because perhaps the biologists don't think of themselves as having to answer the question of causation, so they haven't put a lot of time into it.

But if you were to look today, so where are the criteria of the evidence for making a decision about biological mechanisms, they don't exist. Maybe the experts on the panel can show me where they do exist, but I don't believe they exist.

So, that's sort of in a sense from our perspective, again, looking at general causation, when you say is there a mechanism or not, that's sort of like asking us to sort of open the window onto all of the evidence that

is available in biologyland and saying, yes, I think so, or no, I don't think so, and sort of sifting through that evidence.

Taking an extremely what I will call subjective discussion is anybody who says let me tell you whether or not there is a biological mechanism. There are no rules. The rules -- in fact, we have published on this, and studied it -- the rules go anywhere from I think there is a mechanism, because it makes sense, to you show me the evidence that a certain kind of mechanism exists, and the evidence that this particular factor acts within that mechanism to make the changes that we are talking about, and then I will make a claim about biologic plausibility, or biological mechanism.

So, this is adding to what I would call Steve's epistemic uncertainty. It's extraordinarily non-quantitative, and yet as I mentioned earlier on, biologic mechanism or plausibility is an important criterion from the general causation perspective, and it is typically non-epidemiologic evidence, and there are typically no rules of inference for those, just to add to this sort of epistemic uncertainty.

PROF. POWERS: Can I ask you a question about that, and many of the other comments, but it goes back to a point that we all made earlier. That is, you made the observation that when epidemiology runs out, and judicial judgments begin, you were more comfortable on the one side or the other.

If you read the cases, the cases often make those judicial judgments with some read of what they think science is telling them. What would be enormously helpful is embedded in those judgments, if we can determine are they misusing the science? So, the boundary between those is where we are doing our work.

And, as we go through the discussion, playing out these uncertainties, we meet with opposite reactions, or a variety of reactions. One might be to the extent that the clerks are looking at a model of science, and saying the study shows this, then there is general causation. The conclusion might be it's way more subjective than that. It's way more controversial than that. These studies don't give you confidence to say because the relative risk is over two or one of these other factors, that there is causation.

On the other side, it may very well be that let's

say from people who want more things to go the subjective judgment of the jury, who are delighted of course. You are assuming that within science there are these more clear cut judgments that are quite subjective and judgmental within science, so we might as well let juries make more judgmental -- in other words, these points that you are making that the science isn't from what a lay person would like, not so scientific, not so clear cut. Indeed, it's scientific, but much more of a judgmental point of view.

To identify places where you see from reading the document, places where courts are making those judicial judgments, misusing what their lay view of science is very helpful. I think most courts would be highly enlightened by this discussion, and it's not clear to us kind of which way that cuts.

That science is making more judgments, so courts ought to make more judgments, or is it science is making more judgments, so even the scientific really isn't carry the day. So, that boundary, and it was one that you made earlier, is a really helpful one.

DR. SAVITZ: If I could maybe just react a little bit to that. One of the things I think it's probably important to draw a distinction between sort of scientific and conclusive. That is, in other words, I think that there are very scientific ways to deal with an array of ambiguous evidence. That's where we make a living, is trying to do justice to that.

And I think in practice, even without the rule book, there is no rule book. I think there are certain implicit principles we agree on of consideration, including some of the criteria that were listed by Bradford Hill, but a much broader discussion of the sort of plausibility of the overall story.

And I think I don't know how it plays out in a court setting, but I think that as scientists, and what you might want to draw out here more is a comprehensive, objective description of the state of knowledge. In other words, if you can ease up on us a little bit, don't make us be too conclusive where it doesn't allow that. But allow the injection of the information somehow to tell the story, warts and all.

And that can be done in a very scientific way. It can be done in a reasonably systematic way. And I think that -- I guess I would also say just maybe as a side

comment, I would be careful about trying to use this document to get us to become radically more sophisticated than we now are.

In other words, it's always tempting to say, oh, this would be the place where you should really start using Bayesian methods more. And we should really bring that in, and we should be explicit about our criterion, clean up our act.

I think if you could get us to do justice the field as it now is, it would be progress. If what made it into court was the current sort of state-of-the-art of knowledge and understanding of the science, that wouldn't be bad. Now, I don't know what juries are going to do with it, or judges or whatever.

But I think just trying to make the best knowledge we have, with its ambiguities, with its inconclusiveness where appropriate, have that filter in, and avoid some of the sort of ostensibly scientific conclusive things that as research, are often not doing justice. Now, how you get there, I don't know, but it's a goal at least.

PROF. GREEN: Doug, let me go back. I don't have an answer, but just an observation. You are talking about biological mechanisms. That really has been a struggle in courts in the sense that not so much from the inferential process from an association to causation, but when somebody testifies about an opinion, and of course that's the way in which often this evidence comes in, is somebody comes in with an opinion.

And now what the courts are saying is okay, you may have that opinion, but you have to tell us why. And we're going to take a look at the why, and see whether we think it's adequate.

The biological mechanism is often a part of that. And my sense, my unsophisticated sense, is that often it ranges from being virtually rank speculation – hypothesis -- this is a plausible way in which this could have proceeded, to something far more evidence-based.

The difficulty, and I have no way of knowing how to solve it is for each disease, each agent-disease connection, it is different, and it involves different information, different understanding of biology. I don't know how we can get when this arises, how law, courts, can get access to that, to make an assessment of whether this biological mechanism evidence is anywhere from pretty good,

to very, very speculative.

DR. KASSIRER: Mike, would it be helpful at all to think rather than in terms of probability of causation, would that be of any advance at all? It seems to me that you can -- let's take the situation in which we don't have a lot of statistical data. We are always going to be considering any kind of information that is available, and trying to make a causal judgment.

That information could be temporal associations or biological associations, whatever. We are going to use whatever information we have. And it seems to me, just off the top of my head -- not even just off the top of my head, we have actually thought about this a little bit -- that it may be helpful to think in terms of probabilities, and to ask experts who understand the disease, who at least understand whatever there is to know of the disease, to rate the chance of a causal relationship in terms of a probability.

So, that someone would say well, I think that the likelihood that this is a causal even is 0.25. Or someone might say well, 0.75, and you've got a problem. But you have the same problem when three epidemiologists review the same case and come up with three different conclusions. So, I'm just wondering whether thinking in terms of probabilities would be helpful.

PROF. GREEN: I think it would probably be most helpful in the type of situation that David was involved in where he was a court appointed expert.

DR. KASSIRER: I actually read his testimony.

PROF. GREEN: And certainly there, asking court appointed experts for their overall judgment about the probability, is I guess the way I think probably a court should do that.

DR. KASSIRER: I thought that those three papers, those three opinions where I thought, very interesting because they came to different conclusions. Yet, the reasoning was there for a judge or a jury to examine. So, even though the final conclusions are different, at least the substance of the arguments were laid out, I think pretty carefully.

PROF. GREEN: That's right, and unaffected by the adversarial process.

DR. SAVITZ: Or unaffected by each other, I might mention too.

PROF. GREEN: Right. It would have been interesting then to put the three of you together to see what your composite probability was.

I'm not so sure that using probability -- this sometimes happens with adversarial experts -- is going to be quite as useful as it is when we have people who are not selected by lawyers, and not in the way as in the adversarial system occurs, massaged by lawyers.

DR. KASSIRER: I think one fundamental question which we are not supposed to address, and therefore I shouldn't say this, but the expert witness phenomenon seems to me to be antithetical to science. And the notion of court appointed witnesses, however, seems to me a better approach to understanding the problem.

And the other point is that what you would want to do in getting court appointed witnesses is to identify people who don't have some kind of conflict of interest, who are in a sense, unencumbered by any kind of money. Again, we're not supposed to talk about that.

PROF. GREEN: That's an interesting conversation. It's one we have been having in the legal academy. And there are both practical and political impediments to what many people would think would be a better way to make those decisions. And we can talk about it a fair amount.

We are seeing a little more of it. There is an increase in its use, but by no means is, I think, court appointed experts going to supplant the current system that we have.

DR. SAVITZ: Maybe I can say though, again, I agree absolutely. I know it's grandiose and idealistic, but the goal that I see is to simply reveal the scientific state of knowledge as it stands as clearly and accurately as possible. We have done that. Even if it's still a mess, it's still your problem, in other words, but we have done our job well if we have articulated clearly, and you have really got the flavor, and it's within the range of opinion, reasonably on target.

Again, this may be another discussion, but even for the issues of general causation, where it's not an individual that is being sort of evaluated here, but if there are 20 different courtrooms that are dealing with the general causation issue in the same one, it does seem peculiar that one menu of experts is pushing one way or another, when it's not even the specific causation issue.

But again, as I said, I recognize maybe if anything in here, it's to try to draw out -- if this can sort of in any way, draw out in the process, sort of dislodging people from the biased nature of scientific presentations that can result, of encouraging, at least as we do in practice, revealing the rationale for how we got where we are, and the elements of it.

And sort of the story line, as we have been talking about, about the general causation at least being described more clearly, explicitly. What evidence are you using? How are you using that evidence? What is the sort of description?

Even as Doug said, we don't have explicit criteria or standard criteria for inferring causality, but we are doing something when we do it in each individual instance. And to at least draw out a clear statement of how we got to that and what we are doing. Now, maybe that happens because of the cross examination or whatever. But when we are drawing these inferences about general causation, it would be good to understand how they got to that part of the story. How they sort of laid that out.

DR. WEED: I would like to add something else to what Dave said, and something that was not in your document, but I think you should have it. And that has to do with the extent to which the evidence that is being used in a question of general causation has been systematically collected.

There was no sense in here at all of where was the evidence from? And I'm the reviews editor for the JNCI, Journal of the National Cancer Institute, so if you send a review to me, it better be a systematic collection of the evidence. I always go into the question of general causation from the presumption that the evidence that is available has been systematically collected.

Now, some of it we may decide not to use. This sort of parallels the legal phenomenon from the scientific perspective. But I would like to know where the evidence came from first. And typically, in an epidemiologic scenario for general causation, that is not going to be a study. It's typically going to be more than one study, not always, but typically.

And so that's something I think you really should add to this, is what we usually call a systematic narrative review. It is the systematic collection of that evidence.

Then from that we say, okay, now we are going to look at the 15 case control studies, 10 cohort studies, whatever the evidence is. And we are going to then apply these criteria to that evidence.

And Dave seemed to think that -- it's not that we don't have criteria. It's the way we use them. And there is a subjectivity in there. Let me give you a couple of really classic examples.

In 1996, October, two systemic, narrative reviews came out in the literature on the question of abortion and breast cancer; does induced abortion cause breast cancer? And in one from the Harvard group, the authors said, as far as we are concerned, there is no association here. It's not that there is no causal association. There is no association. Another review published a month later said, 5,000 women year are dying from breast cancer because they had an induced abortion.

So, even within the scientific literature itself, and maybe you guys would like to use one another as experts, but the interesting thing about it was that in both cases, they were using the same general method of general causation that we are talking about. What it sort of underscores within the scientific process, although it's a very extreme example, and there are reasons for it I can explain in a minute.

It underscores that it's not just about criteria, and it's not just about conditions. It's also about what we'll call the personal, social, moral, et cetera, values that people bring into these decisions; scientists as well.

My sense about this, and this is a little bit pie in the sky, Dave, but that's what we do too, is that the objectivity that exists in this thing called science, is tied up in our methodologies. It's not tied up in me personally. I'm not the objective person. I'd like my methods to be as objective as possible.

And when it comes to the methodology of causation, we have about as unobjective a methodology as you can get to. If it could be improved by Bayesian methods, like Steve suggested, I think that would be great. We haven't done that yet. So, what you see is what you get right now. That's all we have on the sort of set of criteria, and the rules that go with them, and subjective values that we throw into this mix.

The final part of that story about the abortion

issue is that one of the investigators had an interview with The Boston Globe a few months later and said, look, I'm an anti-abortionist. I went into writing that review from that perspective. And I wanted the legislators to have some scientific evidence to help them change the laws in Massachusetts, and that's why I wrote that paper the way I did.

DR. KASSIRER: Shame on him.

DR. WEED: Shame on him, absolutely. But like I said, it's a very extreme example, but you can appreciate then if you take out the extreme, and get down into where the center is, where some of those strong emotions or values aren't -- the values are still playing a role in there. And it's because of this methodology that we have, that we haven't improved in 37 years.

PROF. POWERS: Can I ask a question to follow-up? One take is here is somebody who's got an ax to grind, and look at the evidence in a skewed way. But even if that hadn't been there, could you have gone in and looked at this study and said, no, this methodology is just wrong, and this is correct?

I took it from your more general description that putting aside the particular political bias, you would not have been able objectively to say this methodology that got to the 5,000 was wrong, and this methodology that got to the no association was correct, by the non-objectivity of the methodology?

DR. WEED: The methods that were used were exactly the same. It's this method of criteria in which you bring the criteria to bear on the evidence, and assign rules to them as Dave pointed out. You don't even have to tell anybody what the rules are. I don't have to tell anybody what my rule for consistency is to go into an evaluation of consistency.

PROF. POWERS: So that we may now, based on the political statement, have a sense of where this came from, even on an issue that is not so politically charged, I take it the general point is the methods allow for this non-objectivity?

DR. WEED: Yes.

DR. KASSIRER: I actually wanted to make a quick point, and that is that political bias is one thing. Far more frequent is bias related to financial relationships with respect to interpretation of information, not so much

necessarily the methodology itself, although there are plenty of examples where a pharmaceutical company, for example, would help design the study, which is almost certainly likely to come out in their favor.

I'll give you the typical example. Comparing a new drug to a control or to sugar pills, rather than comparing the new drug to the best available treatment. The sugar pill example is going to produce a far better opinion of the new drug than the comparison to the control. But there are plenty of examples in which a bias can be introduced not so much into the data themselves, although that can happen, but into interpretation of the results.

DR. GOODMAN: I guess this follows up on both comments. I think the most important part of the requirement that the analysis be systematic is that everybody has to be very explicit about how they made various critical decisions. So, both in Doug's case, and I was thinking Dr. Kassirer's case, if the treatment of the evidence is systematic, you can, in most cases, isolate the areas of disagreement, and then talk about them.

Otherwise, these discussions often devolve into ridiculous discussions of who's the better qualified expert. And you don't really isolate that one key decision which can be -- and I think this also relates to things David was saying about the scientific method. You might have a completely legitimate scientific disagreement about whether a study should be included or excluded from a systematic review. And that may drive the conclusion.

You could have a very useful discussion about whether it should be included or excluded, and whether in some sense this just adds to the uncertainty, and how much it adds to the uncertainty. That's a meaningful scientific discussion, and reasonable people can disagree, and they can both be respectable scientists.

You cannot have a reasonable scientific discussion several levels above that. You have to focus right on that. But without a very systematic laying out of all the criteria that were used, and when I say all, I mean all, down to the section of studies, why you used these, you can't have that meaningful discussion.

Now, however, even when you get your body of evidence -- I'll tell one little anecdote, pulling aside the curtain a bit on one process I was involved, as many people here were involved in the most recent surgeon general's

report on smoking. I was involved specifically in writing the chapter on causation.

One thing we introduced there, one of the things that was not very ground shaking, was simply to introduce into the conclusions, the same sort of formalism as the National Academy of Sciences uses, that other bodies use, that we should, which actually in prior surgeon general reports, they didn't do to simply classify the conclusions as the evidence is sufficient to claim causality.

The evidence is sort of in an intermediate level, suggestive, but not sufficient. And the evidence is insufficient. Just a three category classification. And also there was a fourth category, the evidence points to no causal relationship.

So, that's the only thing we did. We talked about asking people to provide their probabilities. This was a very crude classification of probability. We didn't even ask people to say what they thought sufficient meant, whether that was in some informal sense 95, 90, whatever it meant to them.

And what we did, we introduced this at the first meeting, that we were going to use this formalism, that at the end of each chapter on each disease that was related, where we were going to explore the relation, do systematic reviews on their relationships to tobacco smoking, that we would ask the authors to classify their conclusions to one of these four.

Because when you look at the surgeon general reports, you find the language of their conclusions dramatically different. And this would be something that would make a lawyer extremely happy. We could trace the language of the conclusions on pancreatic cancer, and on liver cancer, and you would find that it was very difficult actually to figure out what they were saying sometimes. How strong their conclusions were.

So, we decided to use this three part classification at the first meeting of all the authors. It was clear that no one had actually forced themselves to use this. So, we started going chapter by chapter, and going around the table, and making people sort of declare where they fell in this three part continuum.

And I'll just say that that was a very difficult process. People had a really difficult time in many cases, particularly in the middle area. Scientists have a really,

really tough time negotiating within the area --so this is not just in the domain of law -- trying to both express their uncertainty, and sort of commit to it when it's in this intermediate range of suggestive, but not sufficient, whatever you call that range.

And so it's actually in many ways, an artifact of many of the methods we use, that allow us to sort of commit when we are sure above a certain level. But below that certain level, I would tell you that epidemiologists are often at a loss.

And the fact that our methods, when things are significant, or when they are unclear, don't require us to commit to a level of certainty anymore, it also lends to a bit of sometimes -- this is going to be too strong a word -- but a bit of incoherence, or a bit of inarticulateness in expressing the levels of uncertainty below classical levels of surety.

So, I will say that one of the problems that the law is having is that the scientists themselves don't have the tools or the language. And they are not familiar using them, to express and navigate this very, very difficult, sort of intermediate territory, which is exactly the territory where many of these suits are occurring as evidence is accumulating, as you say, you have very little epidemiologic evidence.

So, I want to put some of the -- we are kicking around both professions at the moment. I do want to make it clear that you find confusion because epidemiologists aren't often asked to commit below that certain level. So, you find very, very difficult language to interpret in the studies.

And it's only in the legal arena, when they are forced to apply some more rigorous kind of language to their measure of uncertainties, do they sometimes more clearly articulate what that uncertainty is, and where they would be on this scale of 0.1-.09. Sometimes they might not even agree with themselves, because it's not an exercise skill.

DR. KASSIRER: I think that's the fundamental reason why Bayesian analysis is not going to work. It doesn't work particularly well for clinical medicine, and I don't think it would work particularly well for epidemiology, in part because of the unwillingness, as you point out, Steve, of people to be as precise as they possibly can be about their likelihoods or their

probabilities.

And we actually, 20 years ago, tried to get clinicians to think in terms of probabilities. And to use those probabilities to make clinical decisions. And all I can tell you is that it was extremely painful to do that, and to get them to commit themselves. And we found a fair range.

And the way the clinicians think about relationships is in a kind of a vague sort of way. They think that something may be -- the differences between some of the things that something is likely or unlikely, can be tremendously wide. Actually, it's been studied in medicine, and people just don't agree with what the words even mean.

And finally, we gave up the idea of trying to convince people to use actual probabilities in clinical medicine. My only thought that would be that from the standpoint of looking at causality, that it might be just in itself, a useful approach. But it's a matter of trying it to see if it would work.

PROF. GREEN: Let me point out one of the unfortunate consequences of the reluctance, or maybe the culture that you described. We'll see a study in which the authors conclude that this isn't sufficient to make a judgment of causation, end, period.

And then the case comes into court, and the authors aren't there, but others are, adversarial experts. And then the court is confronted with adversaries about whom it has some skepticism. It goes back to the original study, and the author said, well, this wasn't sufficient.

Now, I don't know what level of probability is sufficient, Steve, but we are very explicit about our probabilities. As you probably know, we have become very explicit in saying 50 percent plus on the civil side. That's fine. We are indifferent about false positives, incorrectly having the plaintiff win, and false negatives, incorrectly requiring the defendant to pay.

And so we have this right at the middle point, is our break. And in many cases we are actually dealing with probabilities in saying this is or is not sufficient. And yet the conclusion of the authors is likely to be taken to mean something less than 50 percent, when I suspect they never confront it or answered that question.

DR. SAVITZ: I really think you are getting into where the issue is sufficient for sort of what purpose. And

in a legal setting, everything is well organized, and we all define what you mean. I'm not even sure what you mean. I mean maybe you mean don't stop funding this line of research, meaning it's not over yet. We don't know enough.

That it's almost sufficient to change policies. In other words, as a generic question, it isn't even one that we ask, or I don't think should ask largely as scientists, and just say generically is this now established as fact? It's not for many purposes, I think a terribly relevant question.

So, I can imagine finding all sorts of things in any paper where in a sense what I worry is you are going to reward the researchers who are most willing to overstate the certainty of their results, because that would be great in court. We know the truth now, and punish those who are appropriately self-critical.

But I just think to me, it's just such a separate arena, what you would say is appropriate. It's not that you are lying in one place, and being honest in another, but you are drawing out the information for a particular purpose, and I think it really does depend on the purpose.

DR. GORDIS: I would just like to cite an experience several years ago that I was mentioning this morning. I came across two papers dealing with maternal smoking and the risk of cancer in the children. They were independently done studies. But the results were very comparable if you looked at the actual data.

And then you looked at the conclusions of the papers, they both concluded that there was no statistically significant relationship between the maternal smoking and the cancer. But they were phrased very differently. One stated there was no statistically different relationship between the maternal smoking and the cancer in the children. And the other one said there was a suggestion or an indication of a relationship, but it had not achieved statistical significance.

Now, that is a very common observation. The visual image that it brings up for me is these poor data struggling up a mountainside, and trying to achieve. And they really disappointed us, because they didn't achieve.

What I say somewhat facetiously is the fact that I think it reflects the preconception of the investigator. If the investigator was expecting a relationship to exist, then he or she is reluctant to accept the statistical

significance. And we can argue about whether it should be accepted, but just to accept it as such, and to just make that statement, the way the first author did.

So, he says, well, it didn't achieve it, but it was there. If we only had a bigger sample size or something, we would get it in some way. So, I think that we have, as a scientific community, have not come to grips with this kind of variability that comes from preconception, even though the methodologies that are described in all these studies, and everything we teach is designed to shield studies from the biases or preconceptions of the investigators.

The fact of the matter is that pretty much every study that is started, is started because of a preconception. You don't just pick a question out the sky to look at. You must have some idea if you are doing a clinical trial, that you think this drug may be better than the currently available drugs. And if you are doing an etiologic study, you think this might be a cause of the disease.

So, we all deal with preconceptions. And the rest of it after that is all designed to shelter the study, when it's conducted, from the preconceptions that generated the study in the beginning. But yet there are so many, as you heard around the table, there are just so many whatever you want to call it, loopholes or whatever.

For example, we train our students, they can recite by rote all the possible biases of epidemiologic studies. And I have had the experience of then saying to the student, well, do you agree with the findings, after they have critiqued the paper, an internal kind of thing. And they said, well, if he had only done the study this way, this way, this.

I said, yes, but he didn't. So, what's your opinion? Are those findings valid? And finally, I gave them Jerry's job. I said, you are the editor of the New England Journal, and you are making a one person decision about whether to publish this paper. Will you publish it as is?

And the students have a great deal of trouble with it. Even faculty have a great deal of trouble with it, because the problem is that we know the biases. We don't know how we can weight them in a standardized, objective fashion. And I think that's the dilemma. And then, if we

enter a courtroom, we are asked to come out with a dichotomous decision.

DR. KASSIRER: The editor's problem is this issue of interpretation. You can be sure that an author, because of their bias, their reason for doing the study, would like to have the study come out positive. Well, I can tell you that we turned plenty of positive studies into negative studies when I was at the journal.

The drug companies, obviously, would like to see their new drugs reported as positive. But there were plenty of instances where an investigator would send you a paper reporting a positive result of a study, when in fact the study was not positive at all. And we would say to them, okay, this is what we think the interpretation should be, which is much more conservative than you think it is. And if you agree with that, we'll publish your paper. If not, send it somewhere else.

The problem is in the editorial office, where the issue that Leon raised just before comes up all the time. That is, it's the data climbing the hill. If we had just done the study for six months more, we would have found, we think, something else. But the study only lasted for a year. And you don't have more than a year and a half data.

So, it really is the responsibility of an editor to try to get rid of that kind of interpretation. The problem is there are not enough editors that the kind of staff that is necessary, or the kind of statistical intelligence in their staff to be able to say, this interpretation is overdone or inappropriate, or whatever.

PROF. GREEN: This is another form of bias, author bias.

DR. KASSIRER: Sure.

DR. WEED: I want to make a comment that I mentioned before. And I want to make sure that if you would like to put it into your descriptive, that you make a very clear distinction between an individual epidemiologic study, and a systematic review of a body of evidence of epidemiology, typically plus biology.

When you use the word study, you have to be very careful. If it's a single study, I'm going to have to say in the field, it will be extraordinary if anybody in the field would take the result of a single study, and make any kind of claim about causation. Oh, they might make claims about association. That's reasonable. That's what it is

all about. That's what you do. But not about causation.

So, it has to be very clear that there are these things called individual studies rolling around. And then there are these things called reviews of the evidence rolling around, in which typically someone else, ideally, although it doesn't always work that way, takes the body of evidence that's been generated, looks at that body of evidence, and then says I'm going to do this for the purpose of asking the question is this evidence consistent with causation or not? It's very important distinction.

There are very important biases -- it's sort of like two levels of inquiry here. There is the individual study in which we have methodologies and biases, and then there is this systematic review of that evidence, which also has its own methodologies, and its own biases. Let me give you a good example of one of those biases.

So, I'm an investigator, and I have done a case controlled study of factor X and cancer Y. And then down the pike a few years later, a journal asks me to write a review of that same evidence. Now, the result of my specific individual study could have been positive or negative. The interesting questions is will my overarching review of that evidence be consistent or not with the result of my individual study?

I actually think overall in our discipline, that those two aren't as closely linked as you might think. But you can find examples of that sort of I'll call it wish science of an investigator. But the important point I want to make is this distinction between the individual study, and the collection of evidence of studies, that we then apply these rules of general causation to. It's a very critical distinction.

PROF. POWERS: Where would relative risk -- I'm more ignorant about this than Mike. Where would things like relative risk -- do those come from individual studies, or are these more global?

DR. WEED: They play a role in both, because in the individual study, you are going to come up with a relative risk estimate from that particular study. And then you are going to have a body of evidence, and your question is if I look at these 15 studies, each of which has its own relative risk value, what is the overall relative risk that I would assign to those studies.

In the old days, that's the pre-meta-analysis

days, that would just be sort -- you sort of take a look at those, and you say, well, they start about 1.2 and they go up to about 3.4, so I'm going to say 2.7 or something along those lines.

These days, if you can apply a quantitative meta-analysis to that information, you can come up with a summary relative risk estimate that is sort of statistically coherent from that body of evidence. It's one of the great I would say positive influences or directions that we have taken, primarily with the single criterion of consistency.

So, in the past, if you had a body of evidence and a bunch of different relative risks, and you would say is this evidence consistent or not? Now, if you apply a meta-analysis to it, and the meta-analysis says, yes, you can put these together and you can come up with that value. You are basically taking care of that single criterion.

DR. SAVITZ: I would just accentuate that. Most groups that have to make decisions, and systemically do so, whether they are recommending clinical policy or other broader health policy, would look for that synthesis of the evidence. And I think that again, if there is any way to sort of discourage -- well, maybe discourage is a little bit too strong.

But where there is this intense reliance and scrutiny, again, I'm thinking of the disparities between life as a scientist and life in the courtroom, and there are these agonizing things over a single study, sometimes a body of research, as though we scrutinize that one enough, and the truth will be revealed.

And I think that most of us would say it needs to be integrated with the broader body of evidence. Now, that's not addressing the point that I think Mike raised of well, what about when there is not much evidence? What about when there is only one study? Well, then that's when you've got it. Maybe it deserves that level of scrutiny, and it deserves a level of caution inherently, automatically, no matter how good it is.

But it is very different than when there is a body of evidence that one can look to, that the confidence I think of most researchers goes up quite a bit when there is this array of information to draw on.

PROF. GREEN: Could I ask a question? It's addressed to the epidemiologists. Would it be fair to say that the concept of meta-analysis is well accepted in your

field, even if there are disagreements about how to do it in a particular case?

DR. WEED: I think it has increased its prominence and acceptance in the field. There are still those who would disagree, but certainly you see it being used more. And I'm very reflective -- very careful to use those sort of observations.

But I think the thing that I would be very careful about, and actually, I have a paper about this, is there is also a trend to overinterpret or overuse the results of a meta-analysis of observational studies in particular, as if to say, as long as we can do a meta-analysis, therefore, the answer is extraordinarily conclusive.

My argument would be just what I mentioned before. We have really only solved one thing, and that is the consistency problem. The rest of it, all the other things that you would want to talk about, strength of association, does response, biological mechanism, temporality, you haven't gone there yet. You still have to deal with those.

And there is a tendency I think, to sort of think if I can get a meta-analysis, I have the answer now. I think you should be really wary of that.

DR. KASSIRER: There is a lot of meta-analytic junk out there too. And I think you have to be very careful, because to do meta-analysis right, you have to be absolutely certain that the individual cases in each study that is involved are consistent, are done in exactly the same way, or very nearly exactly the same way, or else you are accumulating a series of studies that are not comparable, and the conclusions are not valid.

So, the problem with meta-analysis is that there are experts in meta-analysis, and there experts in the disease that is being studied. And very often, the two groups don't get it. So that the experts in the discipline, and the experts in meta-analysis aren't talking to each other as effectively as they should. And you end up with a lot of meta-analyses that are flawed.

PROF. POWERS: I'm told we're supposed to take a break at eleven. So, why don't we finish with Steve?

DR. GOODMAN: I want to say one thing about the real achievement of meta-analysis. I agree with everything here. Meta-analyses are sometimes the most impervious to criticism, and the ones that should be most subjected to criticism at the same time.

But what meta-analysis achieves, which is exactly what you want, is it looks -- and this is just going to rephrase what Doug was saying -- it looks at the evidence in toto. One of the problems that you are confronted with is the language of the statistical methods that we use is not evidential. That is, you get these verdicts. We talk about positive and negative studies.

We talked about error rates, but there is actually no language or measure or concept of evidence in the individual studies. So, as a consequence, there is not a language or concept of cumulative evidence. So, we tend, and particularly in the past, to have taken individual studies of sort dueling claims.

And there is still a lot of that element -- a little bit of it reflected here. But there is a lot of it in the medical literature, where we talk about this study being in conflict with that study. When you actually looked at the quantitative estimates, they are completely consistent in the sense that if you consider the uncertainty, they overlap.

So, there is a long, long legacy of looking at a body of evidence as series of islands, as a series of competing claims. And then you have this discipline of meta-analysis, which says in the broadest sense, no, you don't look at this as a series of competing claims. You look at it as a total body of evidence.

And that's the biggest contribution that the meta-analytic perspective has to your discussion, because it takes this issue of competing studies, competing verdicts, that is, significant and non-significant verdicts, off the table, or it can.

But you do have to recognize that part of your difficulty is not just difficult of generic issue of general versus specific causation. But the mathematical methods we use are not universally accepted, and they have -- I don't want to say universally accepted. They have a certain conceptual baggage that comes with them, and whose liabilities exactly feed into some of the problems that you confront.

And even the scientists themselves often don't literally take the numbers that they generate literal. And yet in a legal setting, it's hard to know what else to do with them, other than take them literally. So, we do have to recognize we are talking about evidence, and yet the

statistical methods, at least when applied to individual studies, don't include the concepts of evidence. And again, that's another gulf between the legal and the scientific realms.

PROF. POWERS: Let's take a break.

[Brief recess.]

PROF. POWERS: I was taken with the exercise -- I think it was Jerry that was talking about going around and asking scientists where you would put this in a category. And part of what I heard this morning was that's difficult from the culture, because of the judgments and the different methodologies, et cetera.

And I wouldn't suggest that you answer this question now, but that kind of exercise from the lawyer's point of view, and from the judge's point of view, would be something like the following. There is a fork in the road. Send the case to the jury or not send the case to the jury. That's where the rubber meets the road for the judge.

And coming to some negotiated compromise between the different cultures, and the different people in studies will say that there is sufficient evidence, or not sufficient evidence, the point about for what purpose, all of that.

If there is an array, for example, of say six or seven individual studies, and one of them on some criteria, would show a causal link -- complex criteria -- others would not. Then you have the meta-analysis. Then the question for the judge is going to be is the state of that evidence sufficient to allow a reasonable jury, whatever that means, to come to a conclusion more likely than not, that there is a causal link?

And the court faces that in a variety of other non-scientific areas. Five people say the light was red. One person says the light was green. And many courts would say, well, if I were a betting person, I'd go with red, but that's enough -- looking at the demeanor of the witnesses, whatever -- that's enough to let a rational jury, that's some evidence to let a rational jury make that decision.

In the similar sense, the question for the judge would be, in multiple studies, some point in a complex way, not just relative risk, but in a complex way, some point yes, some point no. Let's say the meta study points no. The question the judge is going to face, is that enough evidence upon which would let a rational jury make a

conclusion of yes?

I don't know whether --

DR. GOODMAN: Make a rational conclusion of yes, or just make a rational conclusion of yes or no?

PROF. POWERS: Well, yes or no. But if they said no, then the defendant is not going to have any complaint. Would it be rational to let that go to the jury, so the jury could say yes or no? And if the jury said yes, would the appellate court, based on this body of studies, uphold that?

That's kind of similar to the categories you were all describing. It may be that you can't answer that. But that's, from our point of view, what do you do with that?

DR. SAVITZ: If I could just briefly comment. One thing that you do have to watch, and it was alluded to with respect to the meta-analysis, is that at its extreme, it can ignore the substantial methodologic differences across those studies, and just sort of smash them all together.

And there are times that a single study is so strong, and the other studies so weak, that you would get a more accurate impression by focusing your energy on the good study, and ignoring the bad one, which a meta-analysis doesn't do.

So, the question of whether there are situations where -- and this is the problem. It's always going to be this. One can, I think, imagine situations where the counting of studies is positive. And negative would be misleading. The meta-analysis would be misleading. And an obsessive focus on one positive study may be moving closer to the truth.

Now, to make that case, and to make that judgment is a difficult one, but it seems that if someone can make the case, and using reasonable criteria, that it's not a dead issue as the result of the count of the positives and negatives, the meta-analysis, whatever. I can imagine that certainly being something that reasonable scientists and a jury could disagree about.

DR. GOODMAN: I guess I would use one criteria, which is going to sound a lot simpler than it actually is for exactly the reasons that David said, which is I would say that it should always go to a jury or whatever the relative deciding body is if the uncertainty is fairly represented.

Now, that's a very complex -- to me, that's what we've been talking about all morning. But the full

dimensions of the uncertainty have to be represented. And if they are, then presumably an intelligent body of people should be able to make a proper decision. But if they are not fairly represented, that's a different ball game. Of course, you say that the process doesn't necessarily lend itself to fair representation of uncertainty.

But if that's on the table, and if that is there, including the scientific differences and the scientific judgments about which studies are relevant, and why they are relevant, then at least in an ideal world, that is something that I think a jury should be allowed to see. Whether those come out in an adversarial process of course, that's a consequence.

DR. WEED: Let me just take it out of the courtroom for a minute, because I'm trying to think of the analogous situation for us. Is there a sort of minimum amount of evidence that we would consider sufficient for someone to put a review together to write about whether a factor is causal? I actually think the answer is probably yes. I don't know what it is.

Let me put this way. If I were the reviews editor for Epi Reviews or any journal who publishes a review, and someone said sent me a review and said I'm going to review these two studies. We would go, gee, that's not much. You can maybe get away with it.

My sense is that there probably is a sort of minimum body of evidence that we would accept, but I suspect also that it's very dependent on the context. There could be situations and problems that are so important, but the findings, as Dave pointed out, are so incredibly strong that a single study or two, and I think Reyes syndrome and aspirin was a good example of just a few studies.

So I don't think there are any sort of absolute standards, or absolute thresholds for this. But I think the question is a legitimate one to ask. That there may be situations in which we would say there is so little evidence, I don't know what you would say about it. But that's kind of like saying I don't think there is enough evidence here for me to make a statement of causation, which is the reason why I don't think we should talk about it that way.

DR. KASSIRER: There are plenty of circumstances where the data are thin, either because there are no clinical studies, no epidemiology. The courts still have to

come to a conclusion. And in medicine certainly that happens all the time. A new drug comes on the market. Four or five people develop a complication called let's say lactic acidosis. And that's really an unusual complication. Just four or five people have it, yet you want to get that drug away from patients.

Or a new drug comes along and a vascular complication occurs in a specific timeframe. You give the drug. Five days later everybody gets this complication. There aren't a whole bunch of cases. But that timeframe is very limited, and at least from the medical standpoint, you want to get the patients away from that kind of a drug.

There are plenty of circumstances where you are forced to make causal judgments in medicine. And I think the same has to be the case in the courtroom. There are circumstances where causal judgments are going to have to be made without epidemiologic information, in part because you don't have the studies, or because it's just too expensive to do the studies, or because the length of time that elapsed is so long, you can't imagine doing the studies, or whatever.

But still, you have to come to conclusion. And the question is, how do you do that? Well, the answer I think is that it is simply a matter of judgment. And it is a matter of pulling every bit of information to bear that you have available.

So, the issue of re-challenge, you give a patient a drug, and a complication occurs. You give the drug again, and the same complication occurs. That one case is still very interesting, and very telling, at least to a physician taking care of a single patient. But I think it is relevant to the issue of causality.

Differential diagnosis. There is a problem here, not so much in the document, but in the reporters part of it where you talk about rarely is the cause of a disease of clinical significance. That's not so. Doctors look at cause of diseases all the time. I mean if you come in with wheezes and sneezes, the allergist is going to want to know if you have a cat in the house. And if you come in with paralysis of the lower legs, the doctor is going to want to know whether you have had a previous infection.

PROF. GREEN: Is that true for oncologists?

DR. KASSIRER: I wouldn't dare to testify for them.

DR. SAVITZ: I was just going to say that I think it is important to try to put that in. I think it was in there a little, but it could be stronger that where there is relevance to the treatment, or trying to ameliorate the disease, as in the chronic disease, certainly there would be interest.

In many cases, one can think the causes are history, it's over. You just have a clinical condition, and you go forward. But when you have something like an allergy or something like, obviously, it's something to be managed. And so maybe it's important to distinguish those.

The concern I had, maybe the only point I really had coming in here to raise, and I don't know if this is a good time to raise it or not -- I talked to Mike about it briefly -- is discussed on page 7 and a little bit beyond of the differential diagnosis, the differential etiology business. Which is one of the strangest things in a court setting to me.

I want to come there, and they want me to talk about -- I'm there to talk about let's say asbestos and lung cancer. And what they want to do is go through this individual patient. Okay, what else about them is relevant here? We do it on a group level in the sense of confounding.

So, if we have a bunch of asbestos workers, and we want to know if they have an increased risk of lung cancer, well, is it really due to the fact that they tend to be heavier smokers? That would be a relevant question for looking at general causation, or looking at that from a group study.

When you start to try to -- and this came up in the one case I guess you had read, the Parlodel thing. The tendency is to try to use some of the same thought process or logic that goes into differential diagnosis, and apply it to differential etiology.

And I'm still trying to fully understand why it seems to me that it works so poorly. Part of it is that in a diagnosis case there is presumably, I assume if nature cooperates, there is one right answer. And you get it, and you've got it nailed down, and everything else is wrong. So, you knock off the candidates, and you are left with one. I don't know if that really works that way. It's a non-clinician speaking, so it may not even work that way there.

But in this business of etiology, when you say

well, why did this person get disease? And as I was saying before, maybe they got it in part because they are old, in part because they are a male, in part because they have a family history. Unless you have a specific, somewhat complex -- none of those bear informatively on whether this exogenous agent of interest is operating or not.

Under the right circumstances you can lay it out so that my knowledge of other risk factors plays in, depending on your assumptions about the interactions and so on. But it's one of those disparities between the scientific world, where we are interested in of course a constellation of factors. Once you get in that legal realm, scientists think there is this obsession about, well, especially from the side that wants to disprove the cause of interest, what else did it?

And as I said, we don't use things like they got sick because they are old. Well, that's often true in a sense. Or they got sick because they are a male. But then when we get to these other factors, we tend to say, well, if we can account for it by their heavy alcohol use, it somehow exonerates the potential of this other agent being relevant.

I don't know how to draw that out, but as I said, it's just an area that has always confused me as researcher. And I know there is a very specific sort of legal goal in mind there.

PROF. GREEN: That's helpful. I think it will result in our trying to clarify what we think we understand makes sense in the use of differential etiology. And the way in which it might confuse someone where we have multiple causes, either interacting, or multiple causes each necessary for the outcome of interest.

Obviously, the model that is involved here is neither of those. And clarifying that would hopefully make more sense to someone who is reading it.

Let me just say that a fair amount of this morning concerned omissions that you saw in this document, and suggestions with regard to uncertainty, for example, that might be better explained or included. I guess I would like to ask you about some of the things that are in here, like the differential diagnosis that you were just talking about, David.

The question about well, I was talking with Doug during the break about the question of threshold doses and dose response curves. We have just been talking about what

is sufficient when group-based evidence is unavailable. But I fear that that is so contextual, that there isn't much to say other than it's very contextual, and maybe identify some of the things that are already in here.

But what other things that are in here that you read, do you have suggestions, concerns? We are here to hear a critique of this. And in what ways are there statements in here that give you pause, and you think require some modification?

DR. GOODMAN: This maybe is an overly technical issue, but you constantly refer to a multiplicative combination of risks as interactions, in the sense that these two agents are interacting, versus just their effect adding. Yet, the most frequently used models in epidemiology are multiplicative models.

That is, the basic, baseline assumption in epidemiology is that whatever the baseline risk is due to smoking, whatever the risk is prior to the exposure of interest, that the exposure of interest multiples that risk. That's just the methodological assumption when you use logistic regression or the various survival models.

The additive model can be used more, but the fact that that's not used very much. And interactions have a very specific -- maybe you know this if you work in other areas -- have a very specific meaning in epidemiology, which is not the same as the definition you have used here.

The interaction is typically anything that deviates from the underlying model that you are using. So if you are using an underlying multiplicative model, which is the model that most of us use, the fact that two factors that are risks multiple is not called an interaction. That's the expected effect. It's anything over and above that, that is the interaction.

Conversely, if you use an additive model, then anything over and above that is called an interaction. And a multiplicative effect in that context would be an interaction. So, this is a very tricky thing.

So, if we are trying to bridge the divide between the disciplines, you don't necessarily want to use the word interact here for a model that applies to the situation where in epidemiology we say, oh, things are acting exactly as we expect. So, you may want to use different language, or make clear that your term interaction is not the same as what the epidemiologists are using, or whatever.

DR. SAVITZ: I think that is a fair point. I would probably, if anything though -- you are right about the default. I'm not sure that's a good thing. I think it's not a good thing.

For most of the purposes they have in mind, additive definition of independent seems about right to me. You might just want to avoid the word interaction. Just call it a joint effects are additive. The joint effects are multiplicative. The joint effects are whatever they are, because that does often revert back then to the statistical model of an interaction term in a model, which is almost always multiplicative.

DR. KASSIRER: When I first came across the term of general causation, it was something that didn't ring true with me. I didn't quite get the notion of general causation. And obviously, the epidemiologists are quite comfortable with that. And it may be because epidemiologists deal with populations. Physicians deal with individuals.

Now, courts may deal also with populations, for example a class action suit, I suppose, or with individuals. And in the case of individuals, I don't understand what general causality is. I mean it seems to me it's a part of a specific causality. That is, what you are trying to do is nail down whether an individual has the disease or the condition as a consequence of something that happened to them.

And so when you are asking that question, did X cause Y, the first question you have to ask is this issue of general causality I suppose, could it cause Y? And if it couldn't cause Y, then forget about it. But to the extent that you are dealing with an individual, that question, that issue of general causality, is a part of the specific issue of is this particular person's condition caused by this particular exposure or whatever?

So, is it useful to make a distinction about specific and general causality with respect to populations and individuals? I'm not sure. I would be interested in hearing what my colleagues say about that.

DR. SAVITZ: To me, it's interesting to see where, it breaks down, where it breaks down. In other words, there are times that. I think there is a logical sequence to it. And the first question is this agent in general, capable of causing this disease? I guess maybe the reason we like to

break it down, is because we like one question, and we get uncomfortable with the other.

DR. KASSIRER: Because you know how to answer the other.

DR. SAVITZ: At least we know the framework for answering it. And the second part of it, as I said maybe it's not fair, because as you are pointing out, it is for use in a legal setting. We are talking an individual that is being assessed. And it may be sort of in that setting, somewhat artificial, the distinction.

PROF. GREEN: Well, we never made that distinction until we had to deal with all of this group-based evidence that these folks have been producing for us. As this draft points out, in many traumatic injury cases, the notion of a hammer to a head being capable of causing a crushed skull, we know that from long experience, and some better understanding of the mechanisms involved, that there is general causation. We don't even talk about it.

And indeed, I think in some cases, where general causation is well established, and I'm thinking now of asbestos, we don't advert to it, because the only real question in those cases is the specific one, at least with the recognized diseases that asbestos is well accepted as causing.

But it does become, as you point out, it does become a critical matter when we are using group-based evidence in order to try and assess causation. And that is where it has come into the legal vocabulary. And as was said, if we don't have general causation that pertermits any inquiry into specific causation.

DR. WEED: I think it makes a lot of sense. In a sense, it is exactly because I'm an epidemiologist. But I think it's important to mention something that we actually haven't talked about very much, but Jerry you talk about it a lot when you say I'm a physician, and I treat patients, and therefore the question of causation or not, or questions about the individual are relevant.

I think it's important to point out that epidemiology is a part of public health. And that public health has this same capacity for affecter arms as medicine does. That we go out and we intervene on populations. And knowing full well that the intervention is not going to matter for some people. That is, it will have no impact on them at all.

It makes the job of the public health practitioner in a sense, a more complex one, and more sort of ethically ambiguous. We have to be more careful about those interventions. But there are interventions to be made. And they are on a population-basis. And in general causation we come to the question that we want to answer, because as a public health practitioner, we understand there are individuals out there, but we are not making decisions about those individuals.

So, I think general causation in the public health context, as an affecter arm, makes perfect sense. I think it's a good thing.

PROF. GREEN: And it also, of course, plays a role with risk assessment. It becomes very important on the obverse side from what you describe. But that's all in very different contexts from the cases that this document addresses, which is individual cases.

DR. KASSIRER: So, let me turn it around. What do you guys think a judge should do when faced with the lack of statistical information with respect to the kind of available information of the Hill criteria for example, provide?

PROF. GREEN: I'm happy to answer that question, but I guess I should point out that's not really our role here. Our role is not to write what we might publish in a law journal in doing this. We are far more constrained. Our job is to try as best we can, to reflect what is in those decisions that we read, and attempt maybe where we think a court has gone astray, to get it back closer to a straight path.

But we are not free. And I think it's part of the essence of doing a good job at this job, that we try to put aside what we have done in the past, and what we might think is the ideal solution. So, I'll answer the question for you, but we are more constrained than that.

DR. WEED: Can I ask you guys another question? Because something I just heard on the radio this morning. In the state of Louisiana, a case brought against tobacco companies. It's a group claim. It's not individuals. And these folks are not diseased. And they are suing for health care.

Now, it struck me that although we have been talking about the current -- there is this thing called general causation, and there is this thing called specific

causation, and that's about an individual. At least from my sense of what I heard on the radio, this was on NPR this morning, there are going to be cases, maybe there will be more cases in the future, of groups coming to the court.

It's more like the general causation problem, of a group coming to the court. They are not all diseased yet. They just say we may get diseased because of the exposure. And we, as a group, want to get something from them. Now, that is the sort of public health analogy, is it not?

PROF. GREEN: Well, it's the breast implant thing.

DR. WEED: Yes, it's the breast implant. You do have sort of a -- maybe that's not what you guys are doing here today, but it just occurred to me that there is a sort of group claim, and it is about general causation.

PROF. POWERS: Those are quite controversial in the legal system. They are controversial, because the question is whether the injury that these people are suing for, that is the need to let's say be monitored, or to be tested, whether that's a compensable injury.

That's a very controversial, normative question. But if they are, if that is a compensable injury, often the causation issues end up being quite simple. Everybody will agree that having been exposed to this, even if it turns out all the science ends up being wrong, and it wasn't really a risk of being close to a toxin, that you develop cancer or whatever, the sense that you might clearly is putting people at the risk of needing to go get monitoring of some sort.

So, the controversy in those cases could be in the causation issue, but it tends not to be in the causation issue, because the causation issue, one is answered almost exclusively by general causation, and moreover, is just answered by we have this concern. And the causation issue has been answered by that point.

DR. KASSIRER: I wanted to answer my unfair question to you. It seems to me that the courts are going to be faced with those kinds of decisions over and over again, where the data are scattered and not much available, no control trials, no meta-analyses. So, these guys are not even there. So, what do you do then?

It seems to me that what you do is you analyze any kind of potentially causal connection that is available -- biological mechanisms, temporal associations, challenge, rechallenge, even case studies if they are substantive and sufficient. Those data need to be examined in an

unencumbered way by clinicians who deal with these kinds of cases everyday.

And then I think the material has to go to a jury, because the decisions are going to be difficult ones. They are not going to be cut and dried. As you heard here, even when you have epidemiologic data, decisions are not often cut and dried. So, in the circumstances where you don't have those data, then you are going to be left with a much greater degree of uncertainty, but at least some information, some evidence that would be helpful.

PROF. GREEN: And courts are now confronting those kinds of cases. We don't have a lot of guidance on that right now. But increasingly we are I think, narrowing the range of how we are going to treat them. The Parlodel cases are an example of that. We just didn't have any epidemiology on those.

And it is interesting that we had even neutral experts who were appointed, who came to different conclusions, because of a great deal of uncertainty. We have a couple actually of cases involving specific elements in which courts have said, well, there is no epidemiology.

And we sort of understand why, but have engaged in the sort of process that you have, of looking at all events, and saying, yes, this is a reasonable basis upon which to make -- and of course then we cut out the general causation, because we simply can't do it, but to make an individual-based judgment. And there is actually a discussion of those.

DR. KASSIRER: Westbury(?) is a good example of that.

PROF. GREEN: Yes, exactly. That's one of the ones I'm referring to, where we just don't have it, and yet there are some reasonable indicators here that suggest that causation is a reasonable inference.

DR. KASSIRER: I could find myself on the Parlodel cases, to go either way. When I looked at those individual cases, I could look at one and say, yes, this looks like Parlodel caused this. And then I could look at another one and say, well, I'm not sure. And I can see why there is a difference from court to court about the conclusions that they made.

PROF. GREEN: And some, my sense is, disease to disease. There are some different diseases that are involved the Parlodel.

DR. KASSIRER: Yes, that's right.

PROF. GREEN: I think the best example of actually trying general causation in these cases occurred back in the eighties when the drug Bendectin was around. And a judge in Cincinnati tried just the question of general causation for a variety of birth defects. And that was all that went into that trial, was a single question of is this agent capable of causing eight or nine different categories of birth defects at the dosages that humans took them.

That's the only one I know of, but that actually did take place. And of course it resolved an awful lot, although not all, of the Bendectin cases when the jury found that general causation did not exist.

DR. GOODMAN: Another case where I think this is probably going to come up in the absence of epidemiologic evidence is Thimerosal. I'm on the Immunization Safety Board. We have to routinely take up these hypotheses which may or may have evidence.

And this also goes to the issue that Doug talked about before, about whether there is a minimum standard that makes the systematic review worthwhile. Well, what the committee ended up saying was that there is published epidemiologic evidence at all. So, that was an easy call.

But it does a dual review of the evidence, that looks at the epidemiologic evidence from which it derives the causal conclusion. So, in this case, because there was no epidemiologic evidence, the causal conclusion was easy. There was inadequate evidence by definition.

However, it also looked at the biologic evidence. And we had a different classification scheme for the biologic evidence which is very specific to the biologic evidence. It is not the causal conclusions, but it's part of that discussion. It was stated that the theory that thimerosal might cause nerve developmental disorders was "biologically plausible," but the evidence I think was moderate.

That, by the way, is the only thing that has ever appeared in the media, or in the various legal inquiries about this exposure, which as you know, was very hot, that it was biologically plausible. What the committee meant was if you had ever found an association on an epidemiologic level, that was explainable, that was not inconsistent with the biology that says that mercury is a neurotoxin.

It did not say that the theory that it is causing

disease is more likely than not, to be true in the sense that it's been demonstrated. But this, I think, has produced a lot of confusion, and it was unanticipated by the committee, where we were actually trying to clarify the layers of uncertainty. Because we didn't want to hide issues about the strength of biologic evidence that were previously being sort of rolled into the causal conclusions.

So, the question is was the review worth it? Well, I think it's sometimes extraordinarily valuable to go through the exercise of searching very, very hard for epidemiologic evidence, and showing that there is none, or at least none above a certain evidentiary standard.

That is sometimes a surprise to everybody, that there is none. They think there sort of is, but they don't actually know that if any particular criteria are applied, that nothing above -- for example, the criteria may be as simple as there is a comparison group. They may not understand that the only epidemiologic evidence out there is simply a case series, or something that has no evidentiary value.

So, that exercise of looking and finding nothing, or finding very little can be very valuable, if not in the scientific sense, certainly in a legal setting. But this issue of how to handle the biologic evidence, which suggests the plausibility of a finding, should you ever come across it, is a difficult one. I don't know exactly how to deal with that.

That might be a situation in which you make a decision, as this committee did, but in legal settings it might be done differently, saying that if there is no demonstrated human studies, that that cannot go to a jury. That they cannot judge just on -- they cannot extrapolate based on the biologic evidence that might be distant.

And I don't know, but that could be a plausible cut point. One discussion I had in the break suggested this would reward companies or agents that didn't do human studies. So, again, I don't know how to deal with that problem.

DR. GORDIS: Are you using the term biologic evidence to mean non-human?

DR. GOODMAN: I'm using it to refer to mainly mechanistic -- that's exactly right. You could have mechanistic information derived from humans, like looking at a certain pathway. But it wouldn't be looking at the

outcome of interest and exposure of interest in human populations.

DR. SAVITZ: I do need to point out of this gradation of the biologic evidence. I think that's what Leon is getting at too. It may be a different panel that you would want to assemble to deal with situations where there is not sort of direct human studies, with comparison groups and so on.

I have learned as biology advances, anything can be explained. In other words, it's very hard to find some exposure now that we should just do experiments, and just invent randomly a long list, and say is there any plausible pathway. And they will invoke there are some mutant things going on, and there is this change or that change.

That has almost become meaningless in my view, the exercise of saying could you imagine a way in which this agent could cause that disease? Because as I said, as we learn more on both ends, well, of course there is something that would link them.

And trying to deal realistically with the gradient of information there that can be a pretty good, as I think of it, circumstantial evidence that even though we haven't shown it makes people sick, there really can be a compelling case that it should and it could and might, et cetera. Versus the extreme of can you imagine a pathway? And I don't know how you formalize that, but there is a very important I think, gradient there to work with.

PROF. GREEN: If you could give us the algorithm to assess which end of the spectrum it's on, we will give it to the court, so that they can use it.

DR. GOODMAN: You want another panel.

DR. SAVITZ: We'll recommend people for it.

DR. KASSIRER: I would be reluctant to have any kind of cut off based on biological plausibility. I think that's a big mistake.

PROF. GREEN: But how can courts who confront evidence about biological mechanism, how can they assess where on the spectrum that David was just identifying, that evidence exists. And understand you are talking to modern European history majors here about how to go about doing that.

DR. KASSIRER: I think David gave the answer. And that is that what you need is a panel of scientists to examine biological plausibility. As he said you can create

a causal link between the snow falling from the sky and the fact that I have a hoarse voice? Yes, sure, you could find a way to do that. But how about if I have a kidney stone? Well, it would take me a little longer.

PROF. GREEN: But I take it that over time, that evidence will get better and better and be of more value to us in trying to assess whether a causal connection exists or not. Indeed, I hope someday we won't need the epidemiology, because we'll know how things happen.

DR. SAVITZ: Again, when I think of the kind of information that I'm looking for, as I said, I'm very skeptical about the -- imaginative people can do very well in court of drawing these arrows and diagrams. And it only makes sense. And how could anything else possibly happen when you follow it through this way?

But I think of things like if there is truly an animal model that is reasonably well accepted, one for this, and the agent manipulates the outcome, it's a good animal model. Or there are these sort of degrees of when something is mutagenic in a clear way, that really does add to the plausibility that it may be carcinogenic.

And I don't know how to sort of generalize those sorts of criteria, but I assume all other things equal, and others may disagree with this, but the evidence that comes from higher biologic organizational systems like animals, as opposed to cell cultures or even less organized systems, it seems like it gets more analogous to human disease, if you will.

And the degree to which it contributes to known pathways. It's not just saying it might, but if it acts analogously to established causes of disease. There are certain -- again, as I said, I don't know that we are the right group to do it, but I would think that elements of that are done routinely, and could be drawn in to sort of place it, to some degree at least, on the spectrum.

DR. GOODMAN: That's what our panel here does. That's what this whole building is built on, panels that do that.

DR. WEED: I'm just going to agree. I think Dave's got a really good idea to bring some biologists or folks that do this kind of thing to the table. I wouldn't exclude the epidemiologists from that. And as Steve pointed out, that's what we are doing today, because we seem to be the ones who, when it comes to questions of general

causation, we are the ones that are assembled, with others as well.

But typically, epidemiologists are brought together and they say, okay, is this causal or not? And one of the things that we ask ourselves is, so is this biologically plausible or not? And then as I pointed out before, we sort of dip down into the biological evidence, and fish around, and talk to a few people. And like Dave said, we can always come up an explanation.

I think we will need to be there, because I don't think there are too many biologists who are understanding the question, whether it's from our perspective of causation, because we want to do good in public health and preventive medicine. I don't think many of them have a clue about the fact that this legal process is going on, and that they could be playing or have been playing or will play an increasing role in it.

As I pointed out before, the conversation about causation and mechanism in biology is not occurred to much of an extent. You just don't see it. We all go to talks. At the Cancer Institute talks are every other day. There are lots of diagrams and lots of arrows; no evidence at all. It's incredible.

It's like they put these big things up, and every time they put one up, I always want to raise my hand and say, why did you write that arrow there? Is that because there is a study that allows you to put that arrow there? Or is this a rank hypothesis? It might be a really good hypothesis, but is there evidence to support it or not?

I think this would be a really interesting project for you. Last year or the year before, the Institute of Medicine brought a group of us together to talk about biologic plausibility. And I don't know if you guys do anything with the IOM, but they are as interested in this problem as well, because they see it as a great big question mark as well.

There are an extraordinarily few number of places in the literature where anyone has ever even asked the question, if it happens in mice, does it happen in people? Is an animal model, an animal that is done in a mouse or a rat, how is that comparable to humans? In what instances have those studies, if they are in a mouse model, they do occur and can be transferred over to the human situation? It is a vast frontier.

So, I think we don't have the answer, except to sort of point in the direction of what would need to be done. It would be a big project, that's for sure. My sense would be to start with a case study or two of some examples of questions that you would like a specific answer for. Because in the general sense, like you are asking us, I don't think the biologists, many of them, have a clue. I'm not saying that in a pejorative sense. I just don't think they see it as a problem they need to answer right now.

DR. GOODMAN: Although I have to say, a lot of them, when brought into these panels, have an astonishingly strong belief in their theories, and ability to extend them to human populations, where there is no actually demonstrated evidence.

DR. KASSIRER: They have to believe that.

DR. WEED: But it's an assumption about the universality of biological phenomenon that they sort of accept without question, that if it happens, it happens a lot. If happens in this cell, it happen in all cells, without a lot of sort of critical inquiry about that. I don't mean that in a pejorative sense. I don't think they see it as a problem.

DR. KASSIRER: In fairness, the examination of the genome certainly makes you want to believe that even more.

DR. SAVITZ: It's interesting too, the geneticists who do that, talk about the sort of leap from mapping the genome to curing human disease. This is going to be the saving grace of mankind. And, boy, there are a lot of arrows that have yet to reveal themselves, who will make that truly happen.

Now, it's an exciting revolution. It's terribly important information. I think it's another illustration of this leap from the potential and the possibility into wanting to sort of shortcut it and get it all the way out to where it helps people. And if nothing else, we will keep ourselves in business, I guess, because we are worried about the bottom line, what does it do in real people in the real world. And I think you need both lines of evidence, clearly.

DR. GORDIS: I think, from listening to this discussion, we all have faith in the biologic plausibility, et cetera, et cetera. The bottom line to me is that we are going to be left with as much uncertainty, even if you bring a bunch of biologists around this table. And the question

is, how do we deal with uncertainty, whether in the courts or in science?

And I don't think it's going to be obviated by any of the specific methodologic approaches, or what we have talked about so far this morning. We have had epidemiology make findings that were not biologically plausible at the time, and they have stood up very well. They are a minority of the findings, but the relationship of contaminated drinking water to cholera, the rubella malformations. There was no biologic plausibility, nobody knew about viruses, and certainly not teratogenicity.

So, we can cite these as somewhat isolated cases, but we are always going to be left with uncertainty. So, the question is how is the court to handle it? And as I was saying before, it seems to me that it's grounded in the different agendas of the courts and the sciences, or the academic institutions.

In the academic institutions, we like to believe that we are searching for truth. That's what we are all about. And we recognize that any truth today may be changed tomorrow. That is, it's almost an endless process.

In the courts, the courts don't have that luxury, and therefore, there is less of an ability to tolerate uncertainty. I have often said when I've been approached that I would feel much more comfortable about saying something if I could qualify my conclusion with the degree of my uncertainty, but that usually doesn't work out in an adversarial process.

And I think the courts, therefore, have to make a decision. There is also a social agenda for the courts, whether it's through punitive damages to change behavior, or to compensate people when the data are equivocal. I think we saw that with agent orange, in the case that Judge Weinstein presided over. The opinion was very good on what the state of the scientific evidence was at the time, which was very slim. And then he presided, I guess, to decide over settlement, because there was a social mission of the court.

So, I think it's very hard for us to translate what uncertainty does in science, on the one hand, and that keeps us going with a need for another study and another study, to justify or not justify the arrows that have been so beautifully and vividly described here, with the fact that the court needs to reach a resolution. And there is a

plaintiff and a defendant.

And even the issue of animal studies which comes up. I am often asked this question by judges, well, what do I do? You don't have epidemiologic evidence. What about the toxicologic evidence? And I have thought about that a lot, and it seems to me that from the point of view of a public health policy, you might say you want it to be more conservative, that if there is really strong animal evidence, I might take a conservative position and regulate in a tighter way, while we get more evidence or look for it in humans.

But on the other hand, I'm not sure that I would want to allocate responsibility and compensate on the basis of animal evidence alone for human disease. On the other hand, as Bill was saying, you could take it all the way around. At certain times, regulating a substance is going to be so disruptive to a community and its economy and so on, that you may almost be extracting a higher price by regulation than otherwise, than in direct compensation.

So, I don't know how it would weigh out, but it seems to me we have very, very different agendas. And that the answers to a lot of the questions that have been raised in the last half hour to an hour really hinge on what's the agenda that has to be pursued.

DR. SAVITZ: It's really interesting too, Leon is one of the few academics who has delved deeply into this arena. And one of the things that comes to mind is epidemiologists really do want to be useful. And in this case, it's not – it may be nice to say, well, why don't they fix the legal system to make it easier to be an epidemiologist and be helpful?

Realistically, I think we would recognize that it's a matter of us learning enough of how to apply what we know to the greatest benefit of truth and justice and so on. And I think one of the things that is interesting -- I might as well get a plug in -- it really is amazing how little effort in academia at least, is devoted to these areas of application.

Students just hunger for that. Many faculty get involved with it in sort of a disorganized way. If you look around at our faculty, half or two-thirds have been in a courtroom at one time or another.

DR. GOODMAN: As experts, right?

DR. SAVITZ: As experts, right, mostly. I won't

talk about the others.

But I think it would be something that would be fascinating. Again, we are doing a three hour job on it today, but to actually try to work collaboratively to draw this out in the usual sort of plodding, systematic way we tend to do things, which is to deliberate and think and sort of develop even courses or modules or written materials, or whatever.

And again, Leon has written some of those kinds of documents. I think that's a very long-term, big agenda. But I think we agree on that. The prominence of epidemiologic and related information in courts is not going to diminish over time. We are busy churning out new results that will be, for better or worse, making their way into the legal system.

It seems that we might figure out how to somehow do that more effectively. And again, for our end, accepting the burden in part, is for us to be able to characterize this uncertainty. It's a different way than we characterize it in writing the discussion section of journal article. It's a different forum for that. It's not the same audience.

To characterize the state of knowledge uncertainty, again differently than we do in a review paper, which is often setting a research agenda. But trying in fact to do a more accurate job, rather than less accurate job in describing that towards the particular legal uses of the information, something that I don't know how to do, and I think most of us don't know how to do very well.

DR. WEED: I agree. I think it would be an important potential project to work with the legal and epidemiological community, because I think this would force us not only to examine the questions in legal terms, which I think we haven't done very much. But I also think it would force us to examine better, the methodologies and the approaches that we take to this thing called general causation.

Which, as I pointed out, is extremely understudied in the discipline itself. There is a lot of room for progress, and a lot of room for change that would benefit not only the legal community, but the public health community as well.

PROF. MERRILL: I think we have a little time for the people in the audience to have a chance to say a word.

PROF. POWERS: As you are doing that, this has been extraordinarily helpful. It's been a wonderful learning experience for us.

PROF. MERRILL: Let me say on behalf of the Science, Technology, and Law panel here, the people I have talked to from the audience, we share that sentiment emphatically. It's been a learning experience for all of us. It's been particularly a learning experience for me. I teach regulatory law involving toxic material, and that's a territory we didn't probe, but we sort of uncovered the frontier, and maybe we can do another session talking about the science of regulation.

Mike, Lance, do you want to say a word?

PROF. LIEBMAN: Thank you.

PROF. MERRILL: We have three people who have identified themselves as possibly having an interest in saying something or asking a question of the panel. Dr. Linda Fried is from Hopkins, an epidemiologist.

Linda, do you want to take a moment.

DR. FRIED: First of all, thank you. It's been a treat to be able to be in the audience and listen to my colleagues. And I really don't have anything in particular to add to the spectrum of things they have laid out, except to say that I think that there is an interesting and perhaps fortuitous intersection I think at the moment between what might be the need legally to increase understanding about how to adjudicate uncertainty, and the increasing knowledge we have of the complexity of causality, because the more we know, the more problematic this gets.

And there is a point of intersection, I think, with the needs in the scientific community, to understand evidence in a new way. And it might be that the kind of panel that would was brought up could serve both communities very well.

What I mean by that is that in the medical and public health communities, there is a tremendous and appropriate emphasis on the need to translate scientific knowledge into practice. And practice could be assigned variably as clinical practice or public health practice, or policy, or legal practice.

And it's something I thought some about and tried to look into, and we really do not have at this point, beyond the question of causality, we do not have established criteria for when the evidence is sufficient to warrant

translation into the next level of inquiry, or to practice itself.

And I think that that is something that would be very important for the field. And might in fact then be able to inform legal practice as well. And the next level in addition to trying to make sure that you are accurately reflecting the current level of knowledge is to perhaps commission a different level of synthesis than we can do in a three hour session; perhaps in the plodding way it was described. But I think the yield would be tremendous.

The other thing that occurs to me is that there are obviously different levels of evidence. And it might be a useful exercise to try and figure out how to tolerate different levels of uncertainty, or what different levels of uncertainty might suggest in terms of practice.

Obviously, epidemiologic data in some areas, as I think Mr. Powers mentioned, is considered irrefutable. It's the standard, it's so well established, although 20 or 30 years it may not have been. In newer areas of inquiry, it's less well established. And Steve laid out one possible approach to characterizing the level of uncertainty that there is.

And I can see that -- I don't want to say classification system, because they can become so rigid -- guidance system perhaps could be developed as to what aggregate of information that is important to consider given a certain level of epidemiologic uncertainty.

So, I guess what I'm saying is that what's been laid out I think is very exciting and important are the potential next levels of information that both fields happen to need at this moment in time, and mutually could benefit from.

PROF. MERRILL: Thank you, Linda.

Bill Wagner, a lawyer from Tampa, Florida, home of the Buccaneers.

MR. WAGNER: Bill asked a very interesting question, and that is what should a judge consider and do when he is deciding whether to let the matter go to the jury. Much more frequently it's a judge's decision whether or not an expert's opinion that he had, assuming he is not just a hired gun, whether or not that expert's opinion has sufficient scientific support that the jury can even hear the talk.

Or the judge might rule that it is not

sufficiently supported. They are not even going to consider it. It's excluded. I would like to find out their opinions on that problem, because it is a problem that you touched on. I'm not sure judges can solve the problem very easily.

DR. SAVITZ: Maybe I can be more eloquent. If I can just comment a little bit -- I would be interested in what others have to say about it -- in that I had this sort of experience where I had to make that decision about whether -- it gets into these very complex issues of what is sort of scientific reasoning, versus just doing the best you can with whatever you have available. That's science too. We use the information we have.

Maybe I'm just restating the question, but it's really very -- opinions can be sort of well formed. They can be right of course, without a strong sort of scientific basis to them. And the scientific basis I guess to me means that in part, there is at least a thread of evidence. Others can evaluate it. They might not agree with it. But that somewhere back there behind the opinion is an array of information or data that we can all use, and look back to, to formulate that view.

Now, again, I don't know where the threshold should be in a legal setting, but I could imagine that if it doesn't have that, of a sort of base of information to draw on, it seems like it's hard to make inferences -- call it scientific inferences. I mean we make inferences about all kinds of things all the time.

And I guess to me, and again, this is a non-expert in the legal issues, but I can see where if it's just a matter of judging whether the way those inferences were drawn, if it's the right inference and so on, I assume that's what juries are supposed to do. If the basic sort of thought process is legitimately scientific -- I don't know if I'm using the right words in the right technical way.

But to me, that's the big difference. If it's not scientific at all, then it's not scientific expert information. If it is, it can be right or wrong, but I assume that the judge doesn't decide if it's right or wrong. In other words, that's what juries do.

MR. WAGNER: That's what they are supposed to do.

DR. SAVITZ: You can tell me more in practice than I can. I mean, I don't know what it's like in practice, whether it functions that way or not, because as we have been saying, people can tell a wonderful story with little

or no data. As I said, with diagrams and chemical structures.

And if you sort of isolate, where did you get that? Where is sort of evidence base that we can all look back to? It becomes very hypothetical, very theoretical, abstract. And that to me, it's scientific in the sense that it may be a brilliantly formulated hypothesis, but it is not using information that is available to all of us, to draw our own judgment about.

DR. KASSIRER: Could it stand up to independent analysis, is another way of saying what David is saying.

PROF. GREEN: David, I think it would be -- and it is responsive to Bill's question -- it would be fascinating for you to describe the two phases of your views in the Parlodel case in which you served as a court appointed expert.

DR. SAVITZ: I can tell, but I'm not sure I have the two phases organized as well as you do.

PROF. GREEN: I'm thinking about your conclusion about the science, and then your conclusion based on the best judgment. Again, the distinction that you made.

DR. SAVITZ: In this cause it was a case of Parlodel and post-partum stroke. It was not a complete absence of epidemiology. It should be noted there was at least one tiny epidemiologic study that had addressed the issue directly, and basically concluded that the numbers were insufficient for a meaningful inference. That was the conclusion. It was a correct one I think scientifically.

And then there were just vast amounts of mechanistic information that suggested ways in which there could be this link. That it's plausible and it may be there. And the question I was asked is not is there a link or not, because I think as Jerry said, there may be. I don't know. Who knows?

But whether the inference was made on methodologically sound methods, reasoning from data to an assessment that of that, and then a judgment about that data. Sort of in a sense, laying out what is the scientific process, what is a scientifically formed opinion.

And in my assessment of it, and again others could, and did in some cases, disagree, that in the absence of a sufficient base of scientific evidence, it is impossible to draw an inference that is based on science. You can draw an inference, and you can use all the threads

as wisely as any human being possibly can, but when it crosses over into the boundary, at least in my view of sort of a rational judgment, but not one that lends itself to others taking the same data, drawing different conclusions.

Or I should say the methods used to get from those shreds of information to a judgment were not scientific in the ways it was laid out to me. So, I don't know if there is something generalizable about that. But I guess at least I had the impression, and was instructed to some degree, that it is more than just using the best of what is out there.

In other words, that's one thing. You can say, as I said, in day to day life we make decisions all the time. And if we are wise, which we aren't of course, we use the information as well as we can. But not every decision is a scientifically grounded decision. It's just using what we have. And in this case, it was using what they had, and it just didn't lend itself to being couched in the usual scientific terms.

MR. WAGNER: By you.

DR. SAVITZ: By me. And as I said, others could look at that and say no, we think that the -- I'm calling them shreds. I'm giving my value judgment. Shreds of evidence. Others may say, no, there is a solid base here. We have this, we have that. And therefore, we think we have a scientific base.

MR. WAGNER: Help me understand your answer. Was the result of the opinion that you gave that your opinion, and other opinions were considered by the judge or the jury? Or was the result of the opinion that you gave that they didn't hear anything on the issue?

DR. SAVITZ: I was so carefully shielded from the process, I can't describe it as well as others probably can.

MR. WAGNER: What do you think it should be? Should it be that as a result of your opinion, the judge decides that experts should not be heard? Or do you think the results should be that they heard your opinion, and the experts' opinion?

DR. SAVITZ: I don't have an opinion. You are asking what I think is a pretty subtle legal question of whether my view it wasn't scientifically grounded was part of the array of evidence that juries should have access to.

MR. WAGNER: Or the judge.

DR. SAVITZ: Or the judge. Versus saying that it

sort of -- in other words, whether I get to be heard along with others, or whether somehow that opinion is filtered into a process that precludes others from being heard.

MR. WAGNER: I was curious as to what the panel felt should be sort of a minimum standard for allowing an opinion to be heard. I think you expressed it the first time good, but heard two different things.

MS. RELKIN: Hi, I'm Ellen Relkin. I'm the plaintiff's lawyer in that case. And we just got a decision that I was personally displeased with late last week. The court excluded all the evidence. And I should say that, Dr. Savitz, one of the questions directed to you was would credible credentialed experts disagree with you. And I think your answer was some yes, some may, especially those that focus on mechanism such as toxicology and pharmacology.

Which was prescient because one of the three was a very well credentialed pharmacologist appointed, as you were, by the adjudication center, who came out quite strongly in favor of the plaintiffs.

What I found beside losing was the judge really treated this third independent expert I thought very unfairly. He treated him as if he was a plaintiff's expert, not independent. He used words like unscientific. And this was someone who was a pharmacologist. And I think the case is kind of a brilliant illustration of how different disciplines approach these question differently.

You asked Prof. Green about is there an algorithm. Well, pharmacologists do have algorithms. There is one called the Blango(?). There is one where they do look at whether something is induced by a drug, and is it going to give you 100 percent mathematical -- the answer is no. But there are those algorithms that pharmacologists use.

And I think in this kind of dialogue, if we had a pharmacologist, a medical toxicologist, an occupational physician, the type of medical practitioners whose focus is not just on treating on a disease, but on assessing causality, that could add a lot.

DR. SAVITZ: One point, and then I'll let you go on with your other points. But it really does get to the interesting issue of they go right to individual causation. In other words, they are just going right there. This patient, this situation.

It is interesting, and again, I have worked with clinical toxicologists and so on. That's exactly what they

are doing is examining this individual patient, using what is known from the other array of evidence, and making the judgment, without going through the question that we epidemiologists go to immediately, of is there a pattern in which persons who have this exposure tend to have an increased risk of this disease?

And so you are absolutely right. The reason I hate to use the word science is that's such a value laden term of I'm more scientific than you are, or whatever. But I think that it is a very different sort of reasoning process.

From where I sit as an epidemiologist, that's not good reasoning to go from the mechanistic study, to drawing an inference that way. In other words, without the sort of general question of is it -- it's hard for me to understand how they work actually, to be honest, in the sense of looking at one human being, except some of the rechallenge studies, that you could do that a bit. But it's hard to sort of draw inferences from one human being.

PROF. MERRILL: You had another point?

MS. RELKIN: That's kind of the update on that case. Another issue on mechanism, the Institute of Medicine, the Academy here, issued I thought a very interesting report that might be helpful. It was on how to determine the methodology for assessing whether nutritional supplements are safe.

And that's obviously a situation where there is no epidemiology, because no one is funding those type of studies. There are always products on the market that are claimed to do things, and they have adverse events. And it went through a lot of interesting issues, some of the same kind of analysis, de-challenge, rechallenge, temporal relationship, biological plausibility. The type of things one looks at when you don't have epidemiology.

And it was a large group of scientists and doctors that the institute had appointed. You might want to take a look at that.

The last comment I wanted to make was on the differential diagnosis page, which is page 15. Dr. Kassirer addressed it, but I just wanted to add kind of a specific example that just came up a couple of weeks ago in my practice as a plaintiff's practitioner.

I'm involved in a case involving ephedra. It's the diet supplement that is largely coming off the market.

A young woman had a stroke. It's was a very top, top neurologist, one of the leading persons in drug abuse stroke who is convinced that this woman's stroke was from the ephedra.

And he said to me, but I really think you've got to get her to another doctor, because I'm very concerned. She is on a life long coumadin injection. Coumadin is a blood thinner. The neurologist who was treating her, just a local community guy, I guess better safe than sorry, what if she had some kind of clotting disorder, and that's what caused her stroke. So, we'll keep on anticoagulants for life.

Well, this is a perfect example of doctors who assess cause of disease, not just diagnose disease that really happens. Our expert said I'm convinced it's from ephedra, and it is really dangerous for this woman to have to have blood thinner for life, when she is not at risk for stroke anymore.

So, because he diagnosed cause of stroke, that affected the treatment. And he said send her to so and so, who is the head of the stroke department at the university in the city where she lives. And bingo, that guy concurred and took her off the drug.

Now, they are putting themselves on the line. If they were unsure about whether -- well, maybe she's got a clouting disorder, they don't want to subject themselves to the risk of malpractice by taking away this intervention the other doctor had.

So, there really is in the real world of medicine, there are disciplines where they do look for causality, not just diagnosis. And they call that differential diagnosis. I don't think he has heard the term differential etiology. So, there may be some community physicians who don't really look at cause of disease. They just figure out what do they have, and give them antibiotics and send them home.

But there is a whole body of very well credentialed physicians who are more than community physicians, who do look for cause of disease, and I think we should include that type of physicians, similar to the toxicologists, oncologists, et cetera, in this discussion.

DR. KASSIRER: Be careful about your examples though, Ellen, because I imagine that if a patient like that was referred to me, even though I'm not a neurologist, I would first want to carry out some very complicated

coagulation studies to find out whether there is a propensity to clout, and if not, then I would be comfortable about stopping the drug. So, obviously, that's why they were done. And that's why the warfarin was stopped, probably appropriate -- I say probably.

PROF. MERRILL: Does anyone have any other comments?

Let me just make two announcements. The first is to thank you gentlemen, and Steve, who had to leave, very, very much for the time you spent preparing, and the time you spent with us this morning. I think everybody is in your debt. We certainly are.

The other announcement is that the transcript will be on our Web site. It will take probably a month for it to arrive there, maybe a little less than a month. But it will be available to everybody. And as soon as we have a typed copy of that, that will be made available to Lance and to the reports.

Thank you all for coming.

[Whereupon, the meeting was adjourned at 12:45 pm.]