IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)
	)
Plaintiff,	)
	)
vs.	)
	)
ELI LILLY AND COMPANY,	)
	)
Defendant.	)
	)

Case No. 3AN-06-05630 CI

VOLUME 4

TRANSCRIPT OF PROCEEDINGS

March 6, 2008 - Pages 1 through 238

BEFORE THE HONORABLE MARK RINDNER
Superior Court Judge

A-P-P-E-A-R-A-N-C-E-S

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PROCEEDINGS

THE COURT: We are outside the presence of the jury in State of Alaska versus Eli Lilly and Company, 3AN-06-5630. Counsel are all present.

There's a pretrial motion. Lilly this morning has filed a motion to exclude certain testimony of presentation material of Frederick Brancati. I've reviewed that motion and am denying it.

It's clear to me that -- I disagree with Lilly's representation that this has to do with the damages phase of this case. It's very clear to me that this is an indication of side effects and consequences of the disease of diabetes that Dr. Brancati will be testifying on that the slides relate to that and are not case-specific to this case but are more what you might call educational materials or examples in the general sense of those kinds of things and that clearly is relevant to the question of the nature of the disease and the effect that the lack of warnings might have had on sales if diabetes was more strongly revealed as a

consequent, and so I'll deny the motion and -- on that basis.

I've handed both sides my rulings, tried to do this as efficiently as possible, and I thought the best way to give you a response to each of the objections was just to use the objections themselves, and write my ruling on the side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been written on the objections as -- as Roman numeral II, deposition of John Lechleiter was really objections to Denise Torres. Was I correct in that? It all seemed to match up.

MR. BRENNER: Yes.

THE COURT: And, secondly, I will note virtually every question was objected to. I certainly rarely see that in live testimony. But not only was virtually every testimony objected to, but the whole kitchen sink of objections was thrown on them. Given that I'm going to have to clean the dishes, certainly some of those objections really bordered on what I would consider Rule 11 violations. There were some depositions for every case that I suppose would

not be that, but I would just urge in the future that -- make your objections but make sure they're real objections, because some of them don't even -- didn't even come close in this case.

The other thing is I guess I'll just say for the record in reviewing particularly Ms. Torres' objections, I sustained a number of objections, primarily because I felt that a lot of the case related to the off-label promotion issues that I've excluded from this case. As I've indicated, at least on documentary evidence, it's apparent to me that some of that evidence can be used for both purposes, but I felt that the questions were directly pointed and only seemed to relate to the off-label promotion, and that was primarily my basis for overruling -- or for sustaining a good portion of the objections on Ms. Torres' deposition, particularly at the very end of the case, and I just wanted to note that.

MR. ALLEN: Yes, sir. And I -- I'm just now going over them, so I haven't had an opportunity. But let me if I might, just briefly explain. The defense yesterday talked about 23

million users, the severe disease of schizophrenia, saving people from frontal lobotomies and electric shock therapy and its widespread use.

She's giving a misperception to the jury and the fact -- which you had sustained an objection earlier concerning what I wanted to put in evidence that this product became the fourth or fifth leading selling product in the world. So the position that the defense is taking is that Zyprexa was used for schizophrenia and bipolar mania and then she told the jury one other thing yesterday, that it's indicated for bipolar disorder, which it is not.

THE COURT: And when I -- I mean, again, I'm not perhaps sufficiently attuned to the -- to the specifics of some of the things, but there was a question in there that seemed to relate to that, and I think I let -- I overruled the objection on that basis. The other ones were there were a lot of stuff about childhood disorders and Alzheimer's and those kinds of things, and those were the ones I tended to sustain. I believe -- I think I left in the question because of that discussion in the

opening.

MR. ALLEN: Yes, sir. And it is our position. I know you have a jury out and maybe we can look -- I might need to look at this and we can talk about it further. But it's my position they've opened the door. They're giving an inaccurate risk benefit analysis on this drug to the jury because this drug, 35 -- at least 35 to 45 percent -- that's in the testimony of the witnesses. I think it was Ms. Torres', but I can't remember quite frankly.

Thirty-five to 45 percent of the use of Zyprexa was for children and the elderly and depression and indications for which the drug was, in fact, not indicated. And so we're sitting here talking to the jury about we're saving the world from lobotomies and 23 million users. The fact of the matter is 8 million of those would be people that shouldn't have gotten the drug to begin with.

THE COURT: Well, I guess I'll just say this, Mr. Allen. To the extent that questioning later on leads me to think that I can see the questions that are being asked in these depositions as being a kind of mixed evidentiary

or that the door has been opened, you can ask me to reconsider certain rulings but --

MR. ALLEN: Okay.

THE COURT: -- but right now, that's not where we are in this case. And right now the questions and the answers that were asked in that -- on those questions about children, about Alzheimer's about a whole series of questions fell much more heavily in my mind or fell entirely in my mind on the off-label issue that I've excluded from the case.

MR. ALLEN: I understand, Your Honor. One last thing -- 38 percent -- we have the statistics, 38 percent of Zyprexa's use in Alaska, in this state, was not on label. It was off-label, so we have well over a third in this state alone, and I will look at what you ruled and we can take it back up.

MR. FIBICH: Judge, if I may. This is an issue I would like for the Court to be rolling over in your mind today. Because Dr. Gueriguian is going to be testifying tomorrow. Dr. Gueriguian has previously given a report on off-label use. Dr. Gueriguian has previously given a deposition on off-label use.

They clearly opened the door. They stood before this jury yesterday and talked about the risk benefit analysis, that that's what a doctor does. The doctor weighs the living hell of schizophrenia versus the benefits of this drug.

When they did that, they misled this jury because the risk benefit analysis is a lot different for schizophrenia than it is a lady that's having post-partum depression, a child that's getting out of his seat too often in the first grade or the elderly who may be stumbling around with dementia. The risk benefit analysis does not work with those people.

The risk benefit analysis works great with schizophrenia. If you have a truly ill person, you have a risk, you can say, okay, we're going to look at the risk of this drug. When it's someone else, it's a different deal and we're moving the Court that they've opened the door on this issue. We'd like Dr. Gueriguian to testify. I'm not going to take up any more of the Court's time. I just would like for you to be thinking about this, because this will be our motion at the conclusion of the day.

THE COURT: I'm sure I'll be

thinking about it, but I just will say that if the door has been opened, it's not readily apparent to me, at least at this point. If the door is opened, we'll take that up, but right now risk benefit analysis in a general sense is still in a general sense and I haven't heard specific differences of risk benefit analysis coming out or any of those kinds of things nor have I heard the statistics or any of that kind of thing.

I don't have that evidence competently put in front of us at this point, and so I'll just tell you that maybe after today's testimony I'll think the door's been open, but based on -- based on the opening, the door may be open to the bipolar mania issue that was discussed and there was a little bit of colloquy between counsel as to whether it was approved or whether it wasn't approved. But right now, that's all I see the door being open.

MR. FIBICH: We would like the opportunity to talk to the Court about that at the conclusion of today's testimony.

MR. LEHNER: Your Honor, we'd be happy to engage in that conversation if it's necessary.

But I want to ask one point of clarification with respect to the ruling you made with Dr. Brancati. We also raised the point that it appears that he is going to make some comments about the 2007 label. The report that he filed was well before the 2007 label, they never supplemented the report; we've had no opportunity to cross-examine him about any opinions he may be asked about that. I think there was an explicit opportunity to supplement reports as I recall. They did not take advantage of that. I'd ask that any testimony that he's going to give on that be excluded.

THE COURT: Let me ask Plaintiffs if he's going to testify about the 2007 label or -- and if so, how do you get that within your report that was provided?

MR. SUGGS: Your Honor, it's not really a new opinion. Part of the -- it comes in connection with his testimony regarding comparable rates. He's going to testify that based upon his review of the scientific literature, it demonstrates that, in fact, the incidence of diabetes with Zyprexa is higher than with other drugs and that his opinion on that is

confirmed by and consistent with the 2003 ConSensus statement, and further, by the recent label change --

THE COURT: Was he deposed?

MR. SUGGS: Pardon?

THE COURT: Was he deposed?

MR. SUGGS: He was deposed in January of 2007, Your Honor. April of 2007.

THE COURT: So before the 2007 label.

MR. SUGGS: Yes, he was deposed before the 2007 label.

THE COURT: And was there some additional disclosure?

MR. SUGGS: There was no additional disclosure, sir.

THE COURT: I'm going to let him testify as to comparable rates in 2003, but the 2007 stuff needs to not be gone into.

MR. SUGGS: Your Honor, if, in fact, they cross-examine him about comparable rates, would we not be able to -- haven't they then opened the door --

THE COURT: If they open the door, they open the door. It depends what they ask and

whether or not I feel the door has been opened and questions may be asked that will elicit that response, and if I think it's a fair response we'll be able take that up, too.

MR. SUGGS: Very well, Your Honor.

THE COURT: But I'm not going to preclude what the doors open. All I'm going to say is for the time being if he didn't in his report discuss 2007, and there was no supplementation to indicate that, I'm not going to let him refer to matters that weren't fairly disclosed in his report or supplemented or gone into in deposition.

MR. SUGGS: Very well, Your Honor. And if I think the door has been opened, I'll ask to approach the bench so we can discuss it?

THE COURT: That would be the best way to handle it, yes.

MR. SUGGS: Okay. Thank you.

MR. LEHNER: And I have just one question -- just so I have a sense of sort of where the door may begin to swing at what point. I'm assuming he can be cross-examined on comparable rates since that's within his report but if there's some questioning about well, in

light of the 2007 label, how can you maintain this opinion about comparable rates, I would see that swinging the door wide open --

THE COURT: I'm not sure. You 're going to have to fashion your questions carefully. Because what I hear him saying is -- what I understand his testimony is going to be is that you're on notice of that he's going to testify about comparable rates, is that not true? And all he's saying is here's one more piece of evidence that confirms it, and --

MR. LEHNER: Without being able to cross-examine him, what --

THE COURT: And it's a new piece of evidence that didn't exist at the time he wrote his report or at the time he was deposed although there was no supplementation.

MR. LEHNER: But we're in no position to cross-examine him about his view about what this was and he was been given plenty of opportunity to provide those views.

THE COURT: Well, I -- I mean, the test -- just so that everybody knows here, the test I'm trying to apply here is one of fair notice. I don't want trial by ambush and I don't

want people surprised. This is a very close question to me as to whether or not there's any surprise going on.

MR. FIBICH: How can they be surprised about their label? The fact of the matter is --

THE COURT: That's not what the surprise is. The surprise is whether or not this witness was going to offer an opinion or offer testimony about the 2007 label and what it means for this case. That's the question that I'm thinking about.

MR. LEHNER: Well, we'll be careful in our questioning, Your Honor.

THE COURT: You guys -- the Plaintiffs can renew this after we hear cross-examination and I'll -- I'm going to think about this one more. It's a very close question in my mind as to notice. Right now, I'm going to leave it the way that it is, but by the end of the day I'm not sure what I'll do.

MR. SUGGS: Thank you, Your Honor.

THE COURT: Any other pretrial?

MR. LEHNER: I'm sorry -- I'm sorry to take up time, Your Honor. The only other

question is as we've tried to put these deposition pieces together, we did file this motion about the sort of word salad that's kind of going to be created if we can't try to line these up. We'd be happy to show you a little video clip about what we're talking about or --

THE COURT: Well, this is -- you're talking about your motion for clarification of instruction regarding presentation of video deposition testimony.

MR. LEHNER: Yes.

THE COURT: I did think about that last night and this is what my order is going to be: Just as we normally would have -- video testimony is a little bit different because the problem clearly for the other side is that because questions come in orders and in different ways sometimes the context of a clean presentation, if I just weigh it to the defense side is not entirely clear.

And so to the extent there are snippets, as you've -- and that's what I'm going to call them, as you give me an example of that, really either don't give a clear context or where the presentation of just the Plaintiff's side

might really be misleading as to what the witness is saying in the overall context of the deposition.

I will consider applications to have particular snippets of what the defense wants based on reviewing the entire deposition included in the Plaintiff's presentation of that testimony, but that's going to be the only limit. The one thing that I'm really concerned about is because I've seen it many times, is the Plaintiffs designate a very specific, precise series of questions that they want to do, and then the Defendant designates the entire deposition to hide it all, to bury it all and I'm not going to allow that.

The general rule is going to be is that they can present their deposition testimony and then when it's your turn, you can present your deposition testimony. And that's how we're going to proceed, but to the extent I think that doing that will lead to a misleading of the jury or I really think it's a completeness issue so that -- which is really a question of getting the jury a fair picture of what this witness said, that's what I believe completeness is about, I

will consider individual applications on that basis.

But as to -- the general rule will be the rule that was discussed previously that we're going to do this in a staggered fashion just as would happen if the witness were a live witness.

MR. LEHNER: Could I suggest a process then, Your Honor, to make -- to see if we can accommodate that we would designate somebody and the Plaintiffs will designate somebody and they're probably going to have to sit down probably as we speak and try to reconcile these and then just bring to you the parts where we may disagree.

THE COURT: I recognize that that's the implications of my ruling and, yes, that seems to be the best process. The other thing I guess I'll certainly indicate is that to the extent that the Defendants need to replay a few portions of what the Plaintiffs have already played to give them the context in their deposition testimony presentation, I'll allow that as well.

MR. LEHNER: Thank you.

MR. ALLEN: We will --

THE COURT: It will make the deposition a little bit longer, but it gives the -- I want this to be understandable to the jury and I'm trying to be fair to both of you, obviously, and so that's how I'm going to look at it.

I guess what I'll say is I'm going to -- if I -- what I'm very concerned about is the idea of taking what -- some very precise testimony that would be -- might be taken and used in an examination of one side and kind of using the fact that it's a deposition to bury the whole thing, and that I don't like at all.

MR. LEHNER: I don't think that's what we're trying to do. And if somebody on your side can -- whoever's going to be on your side. Is that going to be you?

MR. ALLEN: Let me say that's exactly what they're trying to do. Anyway, we have your ruling, and we'll abide by it.

THE COURT: And is that, Mr. Allen, the process that has been described, is that acceptable to you that you'll get with whom?

MR. LEHNER: And if we're going to

start playing depositions, we need to get people working on this right away.

THE COURT: Right. That actually brings up one more thing. I took care of the two you gave me. Tell me who is next.

MR. ALLEN: I'll get you some more.

THE COURT: Tell me and let me know when, probably you need it by. I hope I have the weekend.

MR. ALLEN: You'll have some more on your desk hopefully this afternoon. As a matter of fact, I'll get that done.

THE COURT: Are they -- again, let me know when you're hoping to play these people so I have my deadline.

MR. ALLEN: Yes, sir. I'll do that.

MR. LEHNER: And we'll look at our objections with your comments in mind.

THE COURT: Okay.

We'll then bring the jury back in, I'll read them some introductory instructions and we'll take it from there. We'll be off record.

(Break.)

THE COURT: Please be seated. We

are back on the record. All members of the jury are present. Good morning, ladies and gentlemen of the jury. Thank you for being here so promptly, and I appreciate your putting up with the patience for the security door. We sometimes have problems because we mess up in our chambers. Sometimes it's because you're still learning the process and sometimes it's because that door just is a pain in the neck.

And I appreciate you putting up with us. If somebody gets trapped between the doors, we will rescue you, I assure you.

But I thank you for your patience and we'll try to make sure it works as best as we can make it work.

Let me give you some instructions before we begin the presentation of the evidence in this matter.

The opening statements are complete and I have explained to you some of the law you should keep in mind as the trial moves forward. The presentation of evidence is about to begin now.

I have already told you that your job is to evaluate the evidence, although I will

be giving you detailed instructions after the presentation, I also want to give you instruction which may help you deal with evidence as it is offered. I will give you those instructions now.

Every person who testifies under oath is a witness. You, as jurors, are the sole judges of the credibility of the witnesses and the weight their testimony deserves. In deciding whether to believe a witness or how much weight to give a witness' testimony, you should consider anything that reasonably helps you to judge the testimony.

Among the things that you should consider are the following:

One, was the witness able to see or hear or know the things about which that witness testified?

Two, how well was the witness able to recall and describe those things?

Three, what was the witness' manner while testifying?

Four, did the witness have an interest in the outcome of this case or any bias or other prejudice concerning any party or any matter involved in the case?

Five, how reasonable was the witness' testimony considered in light of all the evidence in the case?

Six, was the witness' testimony contradicted by what that witness has said or done at another time or by the testimony of our witnesses or by other evidence.

If you believe that a witness testified falsely as to part of his or her testimony, you may choose to distrust other parts also, but you are not required to do so. You should bear in mind that inconsistencies and contradictions in a witness' testimony or between his or her testimony and that of others do not necessarily mean that you should disbelieve the witness. It is not unusual for persons to forget or to be mistaken about what they remember and this may explain some inconsistencies and contradictions.

It is also common for two honest people to witness the same event and see or hear things differently. It may be helpful when you evaluate inconsistencies and contradictions to consider whether they relate to important or unimportant facts. You may believe all, part or

none of the testimony of any witness. You need not believe a witness even though his or her testimony is uncontradicted. But you should act reasonably in deciding whether or not you believe a witness or how much importance to attach to that testimony.

Expert witnesses may testify in this case. These experts may have special training, education, skills or knowledge. In deciding whether to believe the expert and how much importance to attach to their testimony, you should consider the same things that went -- that you would when any other witness testifies.

In addition, you should consider the following things: One, the special qualifications of the expert. Two, the expert's knowledge of the subject matter involved in this case. Three, how the expert got the information that he or she testifies about. Four, the nature of the facts upon which the expert's opinion is based and, five, the clarity of the expert's opinion. As with other witnesses, you must decide whether or not to believe an expert and how much importance to attach to an expert's testimony. You may believe all, part or none of

the testimony of an expert witness. You need not believe an expert witness even if the testimony is uncontradicted but you should act reasonably in deciding whether or you believe an expert and how much importance to attach to the expert's testimony.

You may have exhibits such as documents, pictures or objects to consider as evidence. When deciding how much to rely on an exhibit in reaching a verdict, you should examine its contents and consider how it relates to the other evidence in the case. Keep in mind that exhibits are not necessarily better evidence than testimony from witnesses.

It is possible that I will ask questions of witnesses called by the parties. If I do so, you should consider the resulting testimony as you would any other testimony in this case. You should not assume that because I ask questions, I have an opinion about the case. It is your job and yours alone to evaluate the evidence and to decide what witnesses to believe and what weight to give to testimony.

There are rules of law that present some types of information from being presented as

evidence in a court of law. That is why objections may be made to certain questions of counsel, answers of witnesses or exhibits. There will likely be conferences and legal arguments outside of your presence. I know that you will wonder what is being discussed and after such discussions, why some evidence must be excluded. These matters are governed by the rules of evidence and the rules of the court.

Basically, these rules are designed to do two things. First, they try to help you focus on important and reliable evidence. Second, the rules help you decide the case objectively. We have confidence in the impartiality and the integrity of the jury because these rules ensure decisions based on reliable and objective evidence.

You should not be influenced by the fact that objections are made to questions or to the presentation of evidence or that requests are made that I take certain actions. Nor should you be influenced by the number of objections or requests that are made. Objections or requests are not evidence. You should draw no conclusions about the case from my response to objections or

rulings, as these matters will be determined by the law and will not reflect anything about the merits of the case or my views of the evidence of the witnesses.

My rulings that exclude evidence or bar questions are designed to help you decide the case fairly. Of course, if certain evidence is excluded, you must disregard it. You may not speculate about why the evidence was excluded or what it may have been.

Upon allowing testimony or other evidence to be introduced over the objection of an attorney, I am not implying any opinion as to the importance of the evidence. As stated before, you are the exclusive judges of the credibility of all witnesses and of the importance and the effect of all evidence.

When I sustain or grant an objection to a question, you must disregard the question entirely. You may not draw any inference from the wording of it or speculate as to what the witness would have said if permitted to answer the question.

I have just described the ways that evidence may be presented. Regardless of the way

it is presented, evidence is either direct or circumstantial. Direct evidence, if you accept it as true, proves a fact. Circumstantial evidence, if you accept it as true, proves a fact from which you may infer that another fact is also true. Let me give you a common example:

Let us pretend that as a juror you are asked to decide the following question: Did snow fall during a particular night?

Direct evidence would be a witness testifying that the witness awoke during the night, went to the window and saw the snow falling. From this evidence, you could conclude that snow fell during the night.

Circumstantial evidence would be a witness testifying that the ground was bare when the witness went to sleep at 10:00 o'clock at night, but the next morning when the witness awoke and looked out the window, the witness saw that the ground was covered with snow. From this evidence, you could also conclude that snow fell during the night.

Facts may be proved by either direct or circumstantial evidence. The law accepts each as a reasonable method of proof.

Some jurors prefer to take notes as evidence is presented; other jurors prefer not to do so. Each juror may decide whether or not to take notes. It is not necessary for you to take notes, but it is necessary that you carefully consider all the evidence in the case. Do not let note-taking interfere with your consideration of the evidence. Your primary function is to see and hear the witnesses and observe other -- and observe other evidence.

Each time that you are excused from the courtroom, your notepads must be placed on your chairs face down. When you begin deliberations, you will have your notes with you. But please remember, a juror's notes are not necessarily more accurate than the memory of another juror who chose to carefully consider the evidence without taking notes. When the case is over, your notes will be collected and destroyed.

Our Alaska trial procedure assumes that generally the parties will call the witnesses and question them. As I have told you, it is possible that I may ask some additional questions to fill out a witness' testimony. Occasionally you may be confused about what a

witness meant to say or you may think that a witness has omitted something important by mistake. In most cases these matters will be clarified before the witness completes his or her testimony. If not, you too may ask questions of the witnesses.

Here is what you may do. After a witness has been fully examined by both sides, you should write down a short description of your confusion or the matter that you think was inadvertently omitted on the pad that you have and pass your note to the in-court clerk. As with any question asked by an attorney, I will review the questions you submit to determine if they comport with the rules of evidence and the law of this case. I will also go over the note with the parties.

I may decide that additional questions should be asked by the parties or by me, or I may decide that the witness has testified as well as he or she can or as fully as permitted by law and no further questions will be asked. If I determine that a question is not appropriate or relevant, I may or may not tell you what the question is. I will only tell you

about a question if it is necessary to provide a further instruction about the topic. But if I do not ask a question you submitted, please understand that you are not to draw any inference whatsoever from my decision not to ask that question.

As I have explained to you about questions asked by attorneys, we have evidence rules that dictate what can and cannot be asked. I will treat your questions in the same manner as those of the attorneys, and you should treat my rulings on questions submitted by the jury as you do my rulings on questions asked by the attorneys. Each juror must decide independently whether or not to ask questions of any witnesses. You should not discuss whether to ask questions among yourselves. You should not give answers to jurors' questions a disproportionate weight merely because a juror asked the question.

Finally, please keep in mind that the purpose of allowing you to submit the requests is to help you understand the evidence. You should only ask questions that will help you clarify what you have heard, rather than exploring some theory or argument you might have

concerning the testimony. If you decide to ask questions, you should not allow yourselves to become aligned with any party or attempt to help or respond to any party with your questions. You must remain neutral and impartial throughout this trial and not assume the role of investigator or advocate.

As I told you, this case will probably take about four weeks to conclude. From now until the end of the trial when you go to the jury room to decide this case, you may not discuss this case with or offer any opinion about it to anyone else. This means not with anyone else on the jury and also not with any other person, including court personnel. You are expected to evaluate the evidence independently until you are told to deliberate as a group.

As the case moves along, you should keep in mind that evidence can only be presented a piece at a time. It is common for people, as they hear parts of a story and as they try to make sense of it, to draw certain conclusions about the actors or about the events which go beyond anything they have actually heard. This is natural. However, as jurors, you should

resist the temptation to draw conclusions before you have heard all of the evidence as it may cause you to resist giving fair consideration to other evidence which is inconsistent with conclusions you have already formed.

Under our system, the Plaintiff puts on its evidence and then the Defendant puts on their evidence. In order to be fair to all sides, you should work to keep an open mind until you have heard all of the evidence.

Until the trial is over, you must avoid any contact with any of the persons who are participating in the trial. This includes the parties, the lawyers, the witnesses, and any persons whom you see in close contact with these individuals. Do not conduct any investigations, visit the site of events or research any issue. Remember that you are to decide the case only on the evidence presented here in court.

Do not read newspaper articles about the case or watch or listen to television or radio news stories about this case until the trial is over. Do not read about this case or any matters related to this case on the Internet. If at any time during the trial you cannot see or

hear a witness or an attorney, please raise your hand and I will correct the situation.

If you have a physical or other problem that you would like to bring to my attention, or if you feel ill or need to go to the rest room, please let me know by sending a note to the clerk or by raising your hand, and the clerk will deliver the note to me.

I want you to be comfortable as you carry out your important work. Do not hesitate to inform me of any problem that you have. And ladies and gentlemen of the jury, sometimes I'm very focused on the lawyers or on the witnesses, so if I don't see you raising your hand, Mr. Borneman usually sees you and he lets me know but if we don't see you, please don't hesitate to say, Judge, I have a question. Judge, I've got something that I need to give you a note about. Something like that. If we're not noticing that you've got your hand raised, please feel free to interrupt and let us know that.

I must warn you in advance that there may be delays and interruptions in the trial. Although every effort has been made to deal with matters that may cause a delay or

interruption before trial, there inevitably are matters that come up that must be heard outside of your presence. The purpose of having these hearings without the jury is to ensure a fair trial. I apologize in advance for these delays and interruptions, and I want to assure you they occur only to discuss important matters when necessary.

Is the State ready to present its first witness?

MR. SUGGS: We are, Your Honor.

THE COURT: Please.

MR. SUGGS: Your Honor, ladies and gentlemen of the jury, the State of Alaska calls Dr. Fred Brancati as an expert witness.

THE COURT: And sir, if you could remain standing behind the witness' chair, we'll put you under oath.

FREDERICK BRANCATI,

Having been duly sworn by the clerk, testified as follows:

THE CLERK: For the record, sir, please state your full name, spelling your first and last name.

THE WITNESS: My name is Frederick

Brancati. Last name is B as in boy, r-a-n-c-a-t-i. First name Frederick, F-r-e-d-e-r-i-c-k.

THE COURT: Mr. Suggs.

DIRECT EXAMINATION

Q. (BY MR. SUGGS) Good morning, Dr. Brancati.

A. Good morning.

Q. Where do you live, sir?

A. I live in Lutherville. It's just outside Baltimore, Maryland.

Q. I want to thank you for traveling about 5,000 miles from Baltimore to come here to testify on behalf of the State of Alaska.

Have you ever testified in trial before?

A. Just briefly in a -- in a custody case for the hospital, but never in anything like this before.

Q. Okay. And what is your occupation, sir?

A. I'm a physician and a faculty member at Johns Hopkins University.

Q. And has the State retained you as an expert witness to testify about diabetes and whether or not the use of Zyprexa increases the

risk of diabetes?
A. They have.
Q. And has the State also retained you to testify about whether Zyprexa causes more diabetes than other antipsychotic drugs?
A. They have.
Q. Okay. And have you prepared a report regarding your opinions on those issues and the basis for your opinions?
A. Yes.
Q. And I don't believe you have that report with you, do you, sir?
A. No, I don't.
MR. SUGGS: Your Honor, Dr. Brancati's report is Plaintiff's Exhibit 10127. I'm not going to be offering it into evidence, but counsel have a prior agreement that their respective expert witnesses may have their reports with them when they testify for reference, if necessary.
THE COURT: And that is true?
MR. LEHNER: Yes.
THE COURT: And that's the rule we'll follow.
MR. SUGGS: Very well, Your Honor.

Q. (BY MR. SUGGS) Dr. Brancati, before we talk about your opinions about Zyprexa, I'd first like to ask you some questions about your background, your training and experience in the field of diabetes.
First off, sir, how old are you?
A. I'm 48.
Q. You're married?
A. I'm married.
Q. Your wife is a doctor also. Is that correct?
A. Yes, also at Hopkins.
Q. Thank you. And you have two children? Two 11-year-old girls? Correct?
A. Twins.
Q. And you grew up in Queens, in New York City?
A. Yes, and then Long Island.
Q. I believe you went to undergraduate school at University of Harvard, correct? Or Harvard University?
A. Harvard University.
Q. And you graduated in 1981; is that correct?
A. That's correct.

Q. And you graduated magna cum laude, correct?
A. Correct.
Q. And then you went to medical school after that?
A. Medical school at Columbia University in New York City.
Q. And what year did you graduate from medical school?
A. Graduated in 1985.
Q. And did you then take an internship and residency?
A. Yes, I did, at the University of Pittsburgh.
Q. In what field?
A. That was in internal medicine.
Q. And what is meant by the phrase "internal medicine"?
A. Internal medicine is the training ground for physicians who practice diagnosis and treatment of conditions in -- in adults. Many trainees go on to careers in organ-oriented specialties like cardiology and pulmonary medicine. I stayed in general internal medicine.
Q. And you were in that residency program

from 1985 through 1989; is that correct?
A. Yes, three years of residency and then a year as a chief resident.
Q. What were your responsibilities as chief resident?
A. The chief resident is one of the leaders of the residency program, making schedules, teaching, organizing the practice of the trainees.
Q. And after you completed your residency, did you then go on to get a post-doctoral fellowship in internal medicine at Johns Hopkins University School of Medicine?
A. Yeah. I was interested in research, and so I went to Johns Hopkins for a three-year post-doctoral fellowship. It was in the division of internal medicine and the main attraction was the ability to train in epidemiology.
Q. And that was from 1989 through 1992 that you were in post-doctoral fellowship?
A. That's correct.
Q. Do most physicians in internal medicine have such post-doctoral fellowships that they engage in?
A. Many graduates of medicine residency

programs take special fellowships to train as cardiologists or pulmonary specialists, endocrinologists. Relatively few go into research-oriented fellowships in general internal medicine prevention, epidemiology.

Q. You went into the research side of it?

A. Yes.

Q. Did you also obtain a master's degree in epidemiology?

A. That is correct.

Q. What is epidemiology?

A. Epidemiology is the study of patterns of disease in populations with an aim to identify causes of disease as a means to develop strategies for prevention. It started in the field of infectious diseases and that's where the term epidemics come from. But in the past 30 or 40 years scientists have taken the methods they've learned from the study of infectious disease and figured out how to apply it to chronic diseases like heart disease, obesity or diabetes.

Q. After completing that, am I correct that you joined the faculty of John Hopkins University?

A. Yes, 1992.

Q. Is the John Hopkins University epidemiology program well-known around the world?

A. Yeah. It's one of the biggest and oldest departments around.

Q. And you're presently a full professor of medicine and epidemiology at John Hopkins and also director of the Division of General Internal Medicine; is that correct?

A. That's correct. The -- they'll be mad at me back in Baltimore if I don't make you put the S on the end of Johns.

Q. Sorry.

A. That's okay.

Q. Could you tell the jury what percentage of your time you spend teaching, doing research, doing administrative matters and so forth?

A. Sure. About four years ago I took a division director job. So now about 25 percent of my time is spent doing administrative work for a group of 70 faculty and trainees and students to go along with them. So that's about 25 percent of my time. About 5 or 10 percent of my time is spent in clinical practice, either direct care based in Johns Hopkins Hospital or care

related to the trials that I'm involved in. And then the rest of the time is spent on research and on mentorship of students and junior faculty and trainees who are interested in research in diabetes and obesity.

Q. And how many people do you spend -- how many people do you mentor in their research?

A. It -- it's a lot. I'm indirectly responsible for all 70 faculty in the division, but in my own area of diabetes and obesity it's about seven faculty and about an equal number of post-doctoral fellows and students.

Q. What is the focus of your research?

A. My expertise is in diabetes epidemiology with an eye towards prevention, so I do large-scale studies trying to identify risk factors for diabetes, studying the consequences of diabetes, both established consequences and maybe new consequences, and then I conduct clinical trials either aimed at preventing diabetes or preventing its long-term complications.

Q. Okay. And we're paying you a fee for your -- the time that you spend as an expert in connection with this case, correct?

A. Yes.

Q. Okay. And where does that fee go?

A. I donate the fee to the university to support the -- the research mission related to diabetes and obesity, so --

Q. Do you receive any personal benefit at all for the fee that we're paying for your services?

A. I don't take a lot of money myself, but I get a lot of satisfaction out of supporting the diabetes research effort.

Q. Okay. What is a peer-reviewed scientific journal?

A. Peers -- in science, we use the term "peer" to mean other researchers at other universities who are in a position to review our work, either our grant applications or our papers in an impartial way and give, you know, candid, anonymous opinion about the quality of the science.

So for us the gold standard -- what I train young people there to do is write excellent papers, submit it for review to journals outside the institution. The editors, if they like the paper, will send it out

anonymously to peer reviewers who look at the science, look at the paper, and then make a determination as to whether or not it's valid enough to be acceptable for publication and dissemination.

Q. And why are the reviews anonymous?

A. If they weren't anonymous, the reviews could be quite political. I have a friend somewhere else or I want this other person to think highly of me or this individual is sitting on a review committee for grants I might put in there. There would be a lot of -- there would be a lot of favor exchanged, a lot of -- people who are concerned about recriminations. This way it's perfectly clean. You don't know who's reviewing, and so as a reviewer you can be perfectly candid about whether or not you like the science.

Q. And have you yourself published any articles in peer-reviewed scientific journals?

A. Yeah.

Q. About how many?

A. About 150.

Q. Of those 150, how many had to deal with diabetes?

A. The majority; 120 or so.

Q. Are you a peer reviewer yourself for any scientific journals?

A. Yeah, for many journals.

Q. For how many?

A. Fifteen or so.

Q. And what are national advisory committees?

A. Periodically in science, especially in clinical research, we're called upon by the federal government or by studies mounted by the federal government, the National Institutes of Health, for example, to advise about a variety of matters. It could be about scientific policy at NIH where the federal government should spend its research money.

Sometimes it's -- they call upon us to review grant proposals so that -- the scientists at other institutions have ideas for science that may cost 200,000, 500,000, $1 million. The question is: Is it worth investing? So they would empanel groups to advise about that.

Q. Okay. I think the answer to this question was implicit in your prior answer; but

you've been a member of national advisory committees?

A. Yeah, many.

Q. Did they have to do with diabetes as well?

A. Yes.

Q. Have you been a consultant for any drug companies regarding diabetes epidemiology?

A. Yes, I have.

Q. Which ones?

A. Most recently Pfizer and Novartis.

Q. Okay. Let's talk generally about what diabetes is, how it develops and what the complications of diabetes can be.

A. Sure.

Q. First off, am I correct there are basically two types of diabetes, type 1 and type 2?

A. Yes, there are other types that are much less common. Type 1 and type 2 are the two main ones.

Q. Can you briefly describe what type 1 and type 2 diabetes is?

A. Sure. Type 1 is the less common type. About 5 percent of diabetes cases in the U.S. end

up being called type 1. That's the type that kids and young adults tend to get. They can be quite thin and active. And the problem there is an inflammation of the cells in the pancreas that secrete insulin. Insulin is a key hormone in the regulation of metabolism. And when those cells are inflamed, they cease to work, the body loses insulin, glucose levels go up and they get diabetes. That's type 1.

Type 2 diabetes also involves elevations in blood sugar and blood glucose, but occurs in much different group of people. Type 2, which accounts for 90 percent or so of the prevalent cases in the U.S., tends to occur in middle-aged individuals who are overweight, sedentary. The problem there -- they get high blood sugar, but it's not because the pancreas is inflamed and unable to secrete insulin. The problem with them is that they become insulin-resistant. The body is requiring greater and greater amounts of insulin just to keep pace, and the pancreas fails to compensate. The balance is lost and they get diabetes even though the pancreas is making large quantities of insulin.

Q. Is there scientific evidence demonstrating that Zyprexa is associated with an increased risk of type 2 diabetes?
A. I believe there is, yes.
Q. Am I correct that there is not any type of evidence linking Zyprexa with type 1?
A. There is some data linking Zyprexa to ketoacidosis, which is one of the hallmarks of type 1, but the bulk of evidence that I found was in relation to type 2 diabetes.
Q. Before we talk about the linkage between Zyprexa and type 2 diabetes, let's talk in detail about just what type 2 diabetes is and how it develops.
And have you prepared some slides to show the jury that will help us explain what type 2 diabetes is?
A. I have.
Q. Okay. The first one is entitled --
MR. SUGGS: Hard to hear me or the --
THE COURT: Ladies and gentlemen, are you having trouble hearing the witness?
Thank you very much for moving the microphone. See if that cures it.

Q. (BY MR. SUGGS) The first slide that you prepared is called Type II Diabetes Mellitus. Did I pronounce that right -- it's mellitus or mellitus?
A. It can go either way. I say mellitus. It's from words meaning sweet urine. Diabetes is from a word meaning outflow, and mellitus is from Latin meaning sweet. That's how in the days before laboratories, the condition was diagnosed as sweet-tasting urine or urine that would attract flies.
THE COURT: Mr. Suggs, before we go further, I assume you're offering the doctor as an expert in the field of diabetes?
MR. SUGGS: Yes, Your Honor.
THE COURT: Any objection or any --
MR. KANTRA: As what?
MR. SUGGS: As an expert in the field of diabetes.
MR. KANTRA: I just have a couple questions, if I might.
VOIR DIRE EXAMINATION
Q. (BY MR. KANTRA) Dr. Brancati, you're not here today to offer an opinion with respect to a reasonable degree of medical certainty with

respect to whether or not Zyprexa causes type 1 diabetes, right?
A. No.
Q. And you are not a physiologist, are you?
A. That's correct, I am not.
Q. Which means that you're not somebody who specializes in conducting studies to evaluate the mechanisms by which diabetes occurs?
A. That's right.
Q. So, for example, you've not done studies which would look at -- clamp studies to look at whether a drug might affect a pancreas, for example?
A. That's correct.
Q. And I also am correct in saying that you're not a psychiatrist?
A. That's right.
Q. You don't run a psychiatric clinic?
A. No, I do not.
Q. And you don't make the risk-benefit analyses that psychiatrists and other physicians might make in deciding whether to prescribe antipsychotic medications?
THE COURT: Mr. Suggs.
MR. SUGGS: Your Honor, I think

this goes beyond the scope of what's necessary to --
THE COURT: So do I.
MR. KANTRA: Just establishing the boundaries, sir. With that, my only objection would be that he be offered as an expert witness with respect to type 2 diabetes and not type 1, since he's not offering that.
THE COURT: Any objections to that clarification?
MR. SUGGS: No, Your Honor.
THE COURT: Then I'll recognize him as that, as an expert and will be discussing type 2 diabetes.
MR. SUGGS: Your Honor, the State takes the position that Dr. Brancati is clearly an expert with respect to both types of diabetes. We're offering his testimony about type 2 and that's essentially -- you've heard all the testimony we're going to have about type 1.
THE COURT: Okay. I will recognize him for that purpose.
MR. SUGGS: Thank you, Your Honor.
THE COURT: Go, on Mr. Suggs.
Q. (BY MR. SUGGS) Okay. We were talking

about diabetes mellitus, and I believe you said it was originally called sweet water?
A. Sweet urine. That's where the name comes from.
Q. Sweet urine. You say it was diagnosed in the olden days by tasting urine?
A. Uh-huh, believe it or not.
Q. Thank you. Glad I didn't have that job.
You note there that type 2 is by far the most common in the U.S. How common is it, sir?
A. There -- current estimates is that there are about 20 million individuals in the United States with diabetes and about 90 percent of those, 9-0, are thought to have type 2 diabetes.
Q. Can you track us through the bullet points and explain what you've prepared for us?
A. As I've said a moment ago, type 2 typically occurs in middle-aged, overweight, inactive people. The conventional wisdom is that this is the typical sequence of events. That you have someone who starts off as a young adult who is lean and active, and they gradually gain weight as they go towards middle age. And weight gain -- because of increased calorie intake and

decreased calorie expenditure in the form of exercise and so weight deposits and then that weight gain is associated with insulin resistance.
Q. Sorry. I was going to ask you what insulin resistance is.
A. Sure, sure. Well, for the body to maintain a stable label of glucose, the pancreas serves as a bit of thermostat. It senses the level of glucose or sugar in the blood. As that level rises, the pancreas secretes insulin. And then the response of the body depends on a prompt response to the insulin-sensitive tissues to that signal.
What happens is as people gain weight and reach middle age is they'll develop resistance to that insulin signal or it will take more and more insulin to generate the same response of the body to incorporate glucose from the blood into the insulin-sensitive tissues like fat and liver and muscle. As long as the pancreas compensates by making more insulin, by sending out more hormone, the balance is maintained and the glucose levels stay steady. But unfortunately, in many people the pancreas

fails to compensate. It's still secreting a lot of insulin, just not enough required for that individual to keep glucose levels steady. Then the blood sugar rises and a bit of a vicious cycle steps in, because as blood sugar rises, the function of those insulin-secreting cells becomes less efficient, so they secrete a little less insulin. A little less insulin, a little higher sugar; a little higher sugar, a little less insulin; vicious cycle and then diabetes develops.
Q. Are there early symptoms of type 2 diabetes?
A. There are.
Q. And did you prepare a slide that shows what those symptoms are as well?
A. I did.
Q. What are the early symptoms of type 2 diabetes?
A. So this -- this slide lists a variety of symptoms. Many people will have some and some will have all, depending on their particular circumstances. So one of the cardinal signs is increased urine production. People will notice that they're urinating more frequently, that the

volume of the urine is larger each time they go, that if they've not been urinating at night, they might notice they're getting up at night. If they have been, they might notice that they're getting up more or the volumes at night are greater.
As fluid goes through the body, they become thirsty. The fluid intake -- the body prompts the person with diabetes to consume more fluid to stay even and stave off dehydration.
The other thing that happens because calories are flowing out in the urine. Now the sugar that goes out in urine, that's real calories. It starts to pull calories from the body, and that will lead to increased hunger as if the individual had been exercising and burning calories that way. So people will report increased hunger and they're eating more, but ironically they're more hungry, they're eating more, but they'll have weight loss. Some of that weight loss is from the calories going out in the urine. Some of the weight loss is fluid that's going out being pulled along with the glucose.
As sugar levels rise higher, and as

they become a little dehydrated, they might feel fatigued, malaise, they don't feel right. They don't know exactly what it is. Those are often the complaints that bring them into the doctor's office. A lot of people like the unexplained weight loss because remember, this is going on in people who are overweight. They often interpret it as an unusually successful diet.

So they get fatigue, malaise. Then as their fluid levels drop, they can become lightheaded. And the high levels of sugar and the shifting levels of sugar in the body can affect the way the lens of the eye works and lead to blurred vision.

Q. And is it these symptoms that usually brings a patient into the doctor's office?

A. Yes.

Q. Okay. When they do go to the doctor's office, how do you go about -- have you prepared a slide showing how diabetes is diagnosed?

A. I have.

Q. Okay. And how do -- how do physicians diagnose type 2 diabetes?

A. There are at least three ways. And I'll start at the bottom here because it ties in with

the symptoms. For someone who comes into the doctor's office complaining of increased urine, thirst, hunger, unexplained weight loss, fatigue and so on, all the classic symptoms, if a blood test is drawn that shows that the glucose or the sugar level in the blood is greater than or equal to 200 milligrams per deciliter, that's a concentration in the blood and they have these typical symptoms, that makes a diagnosis. And it doesn't matter whether the blood was drawn first thing in the morning before they ate or late in the afternoon, after breakfast and lunch. That's plenty of evidence and that's how most people with diabetes in the United States are diagnosed in clinical practice.

There are two other ways to make the diagnosis in the absence of symptoms. All of them rely on blood tests. One is to do a fasting blood test. This is first thing in the morning after fasting for 10 or 12 hours. Under those circumstances, the concentration of sugar, glucose in the blood should be less than 126 milligrams per deciliter. If it's 126 or higher, that's evidence for diabetes, even if they're not complaining of symptoms.

Q. Let me stop you for a second there. That 126 milligrams per deciliter, that's 126 milligrams of glucose in a certain volume of blood?

A. Yes. A deciliter is a tenth of a liter.

Q. Okay. And what's the second one listed there? The second test?

A. The second one listed there is used most often in research studies. This is a definition based on an oral glucose tolerance test. This is used most commonly in clinical practice in the United States for pregnant women, otherwise we don't do many glucose tolerance tests. The idea there is that if you want to pull out all the stops to make the diagnosis, you don't rely only on the fasting glucose, because that can hide levels of hyperglycemia occurring during the rest of the day after meals.

So what's done in the oral glucose tolerance test is you give the patient a very sweet drink that is very syrupy, about 75 grams of sugar in it. They swig that and you measure the blood sugar just before they drink it, and you wait two hours later and measure again. If they don't meet the fasting criteria for

diabetes, they could still meet it in two hours. In someone who doesn't have diabetes, two hours after the oral glucose is taken, their blood sugar should be less than 200. If it's 200 or greater, that's evidence of diabetes. Diabetes you may not have found just by testing the fasting sugar.

Q. Thank you. Do you have some slides that show how the body converts food to sugar and the role of insulin in this process?

A. We do.

Q. Okay. I notice that this slide has a legend down on the bottom that says, Look Ahead, Action for Health and Diabetes. What's that mean?

A. This was a slide I took from one of the NIH-funded studies that I work on. This is a test -- this is a study, ongoing study designed to determine the long-term health benefits of weight loss in people with diabetes. We have a teaching module in the trial for the purposes of bringing people with diabetes up to date, and this is one of the figures that we use.

THE COURT: Doctor, you used the term trial, I think, twice -- I think. You're

not talking about us today, right?
THE WITNESS: That's correct. In scientific medical jargon, a trial is an experiment in humans, and typically the design is you take a group of people at risk for some complication. In the case of Look Ahead, we have people with diabetes at risk for heart disease. We flip a coin and assign half the study participants to one condition. In this case, it's just their usual care. And we flip a coin and assign the other group of individuals to another question and Look Ahead, it's intensive coaching about weight loss.
And then the trial component, you follow both groups forward over time and you look for systematic differences in the occurrence of those complications.
THE COURT: Thank you.
MR. SUGGS: Thank you, Your Honor.
Q. (BY MR. SUGGS) This chart shows at the top, food in the form of carbohydrates going into the stomach and then apparently getting converted to sugar.
Is it only carbohydrates that are used by the body to make sugar?

A. We show carbohydrates here because that's the constituent of the diet that's most directly converted to glucose, but the liver, part of the liver's job in the body is to be a clearinghouse for all different types of food substances. And part of what the liver does is it can take protein, convert it to carbohydrate; take carbohydrate, convert it to protein; convert both of those to fats. That's the liver's job but we just show carbohydrate here as an example.
Q. Can you walk us through the chart starting at the top, and how the body processes food.
A. Sure. So this is north in the body. This is south, so people eat food, it goes into the stomach. It's acted on by digestive enzymes and for carbohydrates that releases a lot of sugars into the blood system. So this tube here represents the blood system around the gut. The S's represent molecules of sugar or glucose. The I represents molecules of insulin.
When sugar is released into the bloodstream, that signals the pancreas to act. This is the pancreas, it's about the size of your fist, and it sits back behind the pit of the

stomach. We usually don't think about it much. Much of the substance of the pancreas is devoted to making pancreatic juices, enzymes that help digest foods, especially fat. But if you slice it and look under a microscope, you see small islands of cells.
They're actually called islet cells. And they're the insulin-secreting cells of the pancreas. They're very well-positioned to sense the levels of sugar in the blood and so they're poised to respond quickly. When the sugar level goes up, the insulin secreted by the pancreas -- the insulin goes all over the body through the blood supply. And it specifically triggers three types of tissue to take sugar or glucose out of the blood and into that organ. And those insulin-sensitive organs are liver, muscle and fat, fat all over the body.
Q. How is it that insulin regulates the activity of sugar or the presence of sugar?
A. For these three types of organs, sugar can't get into -- can't get from the bloodstream into the organ without insulin more or less unlocking the door.
Q. Do you have a slide showing that?

A. Oh, yes. Yes, I do. So, in fact, here's the lock and the key. These are fat cells, a rim of cell, and then a big fat droplet on the inside. This is sort of the way they look under the microscope. And even if there's sugar bathing that tissue, it won't go in unless there's insulin there to send a signal to the cell to actively take the sugar from the bloodstream into the fat cell. If there's no insulin circulating, as in kids with type 1 diabetes, who get inflamed pancreases, that's a problem where sugar will build up in the bloodstream and cause diabetes.
In people with type 2 diabetes, there's plenty of insulin floating around. The trouble is some of the keyholes are blocked and it doesn't signal properly and the sugar backs up into the blood supply for that reason.
Q. And what is it that makes those cells resistant to insulin?
A. That's a great question. There's still a lot of active research on that but we know a lot more than we did ten years ago. When I was coming through training, the thought was that, for example, fat tissue was really inert. It was

just a storage depot, just a place to keep energy in the form of fat and, you know, wasn't otherwise very active in regulating the metabolic machinery of the body.

Now we know that the fat cells secrete a variety of hormone-like substances, small molecules called adipocytokines. They flow out of the fat cells into the blood. They circulate around the body and they change a variety of things. They can change behavior. They can influence appetite. They can influence the way the liver responds to insulin levels. They can affect the way the fat cells themselves respond to insulin.

So there's intense interest now in identifying those molecules, and there are many of them, in an attempt to develop drugs that might influence the way fat leads to insulin resistance.

Q. So weight gain, is that related to insulin resistance?

A. Yeah. So a lot of evidence from a variety of sources that weight gain or adiposity itself -- people who are already overweight or obese, that those individuals are much more

likely to have insulin resistance than leaner individuals.

Q. Okay. And is it fair to say that if the body becomes insulin resistant, the sugar that's in the bloodstream does not make it into the fat cells and just remains circulating in the bloodstream?

A. Exactly. So that's what's thought to happen when you see blood sugars rise from the normal range, which might be in the 80 to 90 range. And they -- they rise -- they can rise to 100, 105, 110 as -- still not in diabetic range, but now in that 100 to 125 range which we call impaired fasting glucose. Those are individuals who seem to be on their way to getting diabetes, and it's a high-risk group that's been targeted by public health agencies and the federal government in diabetes prevention strategies.

Q. Earlier you were talking about the diagnosis of diabetes by looking at the blood levels of sugar. Is it fair to say that those elevated blood levels then are the result of insulin resistance, such that the sugar doesn't go in the blood cells and is staying in the blood?

A. Yes, in the majority of cases, those elevations of blood sugar in middle-age, overweight individuals is related to the insulin resistance.

Q. Is -- when the blood has higher levels of sugar in it than normal, is that referred to as hyperglycemia?

A. Yeah, hyperglycemia can refer to increases in blood sugar across a whole range. So, for example, in the general population a normal level in a middle-age adult might be 85 or 90. For that individual, if they go from 85 to 90 to 105, they're showing some degree of hyperglycemia because it's high compared to where they were or it's high compared to a normal population.

By the same token, if you talk to an endocrinologist, 105, that's great control for someone with diabetes. Hyperglycemia in kids with diabetes might be 300 or 400. It all depends on where you're starting. Hyper, depending on the study or setting, means higher than expected or higher than before or too high for safety.

Q. I've heard doctors sometimes talk about

signs and symptoms. What's the difference between the sign and the symptom?

A. A symptom is a complaint, so that depends on the judgment of the patient. And given the same sort of physical conditioning -- physical condition, two patients may have very different symptoms. Someone who is very stoic will have no symptoms even if they're having terrific metabolic derangements.

A sign is something objective measured by the physician. Could be a physical sign, something they find on exam. The skin is dry, the membranes of the mouth are dry and make a diagnosis of dehydration, or could be -- it could be from examining the chest with a stethoscope. Those sorts of things are signs.

Q. Okay. And is hyperglycemia a sign of diabetes?

A. Yes. So you can also have signs that are obtained by laboratory assessment, kind of an extension of the senses of the physician.

Q. And if you see hyperglycemia in a patient -- you had some levels before there that were diagnostic for diabetes. If you see hyperglycemia at those levels, is that a sign for

anything other than diabetes?
A. No, unless they happen to be in the hospital and have glucose running intravenously and have some external source of blood sugar then in clinical practice it's really diabetes mellitus.
Q. Thank you. So would it be fair to say that if you did a randomized study where you gave one group of patients a particular treatment and after that they then showed -- that group showed hyperglycemia, what would you -- what would you take from that?
A. If it's hyperglycemia in the frankly diabetic range, 126 or greater, then I'd conclude that the drug is provoking episodes of -- of diabetes. If it's -- if it's hyperglycemia, still in the nondiabetic range, it would make me worry that the drug is pushing individuals from a normal state to insulin resistant to impaired fasting glucose on the way to diabetes, but maybe not yet.
Q. We talked about how hyperglycemia occurs in diabetes. Why do we care if somebody is hyperglycemic? What's the result of having too much sugar in the blood?

A. Well, I mentioned some of the short-term problems which could be troublesome, but the real problems is with diabetes in general type 2 diabetes, in particular, are the long-term vascular complications, the damage to the large and the small vessels in the body.
Q. Do you have a chart or slide rather, that summarizes that?
A. I do.
Q. Actually, before we get to that -- I take it back, let's go right there.
This slide that you prepared is entitled, Diabetes Leads to Long-term Health Problems and Death by Damaging Blood Vessels. And you've got two headings in there. The first is macrovascular disease.
Can you explain what you mean by that phrase macrovascular disease?
A. Well, let me make the contrast between macro and micro. Macro is a prefix that means big or visible to the naked eye in this case; micro means small or too small to be seen by the naked eye. You need a microscope. And vascular means blood vessels, or the tubes that carry blood. So macrovascular disease is the type of

blood vessel disease we can see in vessels -- vessels we can see with the naked eye. We can see the disease with the naked eye. So when we go to medical school and we dissect, we learn. We can see the vessels of the heart, the coronary arteries; we can see the vessels that lead to the brain, the carotid arteries; and the vessels that lead to the leg, the femoral arteries. And macrovascular disease is the term that diabetes researchers use for what other physicians and researches call athersclerosis or blockage of the arteries from cholesterol deposits, inflammation and superimposed clot.
Q. And is there a higher incidence of macrovascular disease in diabetes?
A. Yes, there sure is. Macrovascular disease can occur and does occur in people without diabetes. The trouble with -- the problem for people with diabetes is that they have a much accelerated process compared to nondiabetic individuals. They are at much higher risk.
Q. And do we know why that is?
A. A lot of different theories, but like everything else related to diabetes, it's

multifactorial. Some of the theories have to do with modification of the cholesterol which is involved in creating the blockage so that it's more likely to deposit. Another line of reasoning has to do with inflammation inside the body, really around the body in such a way that the -- that the smooth lining of the blood vessel is damaged or creates an area for deposition of cholesterol.
Another theory has to do with the effects of high blood sugar on platelets, the small elements in blood that are involved in forming clots. So there's a variety of different pathways to atherosclerosis.
Q. You've used the term atherosclerosis now a couple of times. Do we have a chart or actually a picture that shows that process?
A. We do.
Q. Can you tell us what this depicts?
A. Sure. So this is a cross-section of, say, a coronary artery. So this would be if you have the artery like this and snip it and look at it down longways into the opening. This is what you'd see in a normal vessel. Three layers of tissue here, the endothelium here and the blood

would pass through the lumen or the open part. You see here it's nice and clear and the blood can pass through at high speed.

What happens in atherosclerosis is that there's damage to that lining, to that endothelium. And then inflammation around it. That brings inflammatory cells to the area, cells that attract cholesterol and various other material. The cholesterol begins to deposit, first at the inflamed site and then all around the vessel. You can see as this plaque forms, this area of gunk underneath the endothelial lining, the lumen, the open part of the vessel begins to contract markedly. Now whatever is downstream from that vessel is at risk because the body can't deliver blood and oxygen and nutrients to the same extent as before.

This might be the case in someone with chronic stable angina. So take someone who says that when they're at rest they feel fine. They go up one flight of stairs, they're okay. Try two or three flights, they get short of breath, chest discomfort, they get winded. That would be the circumstance here. They can only deliver so much blood and oxygen to the heart.

As soon as they're below that requirement, they're okay. As soon as they push beyond it, they get symptoms.

That's bad; but this is worse. Here's the plaque and now there's a plug of clot right over it. This is what happens in someone who has a heart attack, or the technical term is myocardial infarction. They're feeling fine, they're going about their business and then all of a sudden, maybe without any particular exertion or change in their circumstance, sudden crushing chest pain, shortness of breath, sweating, collapse. That's because all blood flow is suddenly stopped because of this clot that's now plugged the vessel and leading to death of the downstream heart muscle.

Q. Why does a clot form?

A. Part of it, as the plaque forms and the inflammation occurs, it begins to attract platelets, the cells that form clot. And as -- as that inflammation progresses, the risk of clot gradually increases. Also the space inside the vessel is contracting, so if there's any clot that starts to form, it doesn't take long for it to fill up the remaining space.

Q. Okay. And can this atherosclerosis occur anywhere in the body?

A. It can occur anywhere. We're most concerned about when it occurs in crucial vascular beds, the blood vessels that lead to key organs. The three most important and commonly affected are the brain. When you get this in the vessels that lead to the brain, you can get stroke. When it occurs in vessels that feed the heart, you get heart attack and when it occurs in vessels that go to the legs, first you can get claudication, pain with walking, but then that can progress all the way to gangrene and the need for limb amputation.

Q. Okay and did you bring some slides that show atherosclerosis in the heart?

A. I did.

Q. Will you turn to that next. Can you describe for the jury what this depicts?

A. Sure. Here are some of the -- here's the heart and this is the meaty part of the heart, the chamber that does the pumping, and it has three main vessels that feed it. And here's a diagram of one of those vessels and this shows the development of atherosclerosis in the vessel.

Now, instead of looking at the vessel end on, it's been unroofed and you're looking along the long axis of the vessel and this is what you could see with the naked eye. You'd see this yellowish, cholesterol-laden plaque constricting the lumen or the open part of the vessel. And in this diagram there's a clot there. So this is what we see in someone who's had a heart attack.

Q. And in that vessel there, I've heard some people -- my father had a coronary artery bypass. Was that this type of process that was involved in it?

A. Sure. Once there's a clot, there's a heart attack and there -- and the horse is out of the barn a bit. But before there's a clot, the individual may be having symptoms with exercise; but at rest is doing okay. They get evaluated and the cardiologist finds several blockages, but the blockages are close to the beginning of the arteries and downstream things look clear. In that circumstance one can take a mechanical approach to the -- to the blockage. One mechanical approach is to bypass it; take part of the vein from a leg, hook it up upstream from the clot, downstream from the clot, just bypass.

That's what a coronary artery bypass surgery is, or coronary surgery is.

Another approach is to lead a small plastic catheter tube from the leg, up into the vessels, back into the vessels, and then inflate a balloon inside the blocked area. The balloon presses the plaque up against the side walls of the vessel, opens it up more. That's angioplasty. And typically today, following angioplasty there's stenting, which is the placement of a small metal coil or mesh in the area that's been ballooned to keep it open.

Q. You said this type of process could result in a heart attack. I've also heard the expression myocardial infarction or MI. Is there any difference there?

A. All the same.

Q. In the myocardial infarction or the heart attack, is that where the blood vessel gets plugged up with the clot like we saw in the other diagram?

A. Exactly. And then everything downstream from that -- from that plaque and clot is at risk and will be initially stunned and then deprived of blood and oxygen, will actually die off and

scar.

Q. Okay. You said that also this process can result in problems with the brain.

Do you have a slide showing that as well?

A. I do.

Q. What does this slide depict?

A. So here's a cross-section of the brain. This is the neck and the ears and the head. The carotid artery comes from the heart, from the aorta down here. There are two main carotid arteries, one on each side of the neck. You can feel if you press, the pulse here. That artery tends to develop atherosclerosis. When it does, it can cause trouble in two ways.

One is that if clot forms on top of the plaque, the brain downstream from the carotid -- down from the blockage will die and that's called a stroke. So that can happen either because of a blockage down here or it can happen because a small clot forms, blood clot can pass here, but the clot breaks off, runs upstream and lodges in the smaller vessel there.

Or a part of the plaque runs here, runs downstream and lodges in the smaller vessel.

And then you typically see this wedge-shaped triangular area of stroke or death because all the branches of the vessel downstream will be occluded and the part of the brain fed by those vessels will die.

Q. Okay. And I believe you said also that this type of atherosclerotic process can also affect limbs; is that correct?

A. That's correct, especially the legs.

Q. And do we have a diagram that shows that as well?

A. We do.

Q. Tell us what is shown on these pictures.

A. Here's the leg. Here's the femoral artery. This is if your doctor's ever felt for the pulse down in the groin, they're feeling up here. They're feeling the pulsation through that artery. It's a big one. Normally it's wide open and it needs to convey a lot of blood and nutrients, but the leg is a big chunk of tissue and quite active. When atherosclerosis occurs, there's blockage of that big vessel. It's big enough that there's no -- the first people will get is pain or limping or cramping with exercise. So someone will say, when I'm at rest, it's fine,

when I'm walking slowly for a block, it's fine but if I walk two blocks quickly, my legs will cramp up. I'll get pain in the calves and I have to rest for five minutes, then I can walk again.

Q. What is the end stage of this particular problem in the leg?

A. The problem here is that the leg gradually becomes more and more ischemic. It's getting less and less blood and less and less oxygen. And that -- that predisposes to infection and infection can be very severe if the blood -- if the body is unable to deliver oxygen and nutrients and inflammatory cells to the involved area. As the blood supply is closed off, there could even be death of the tissue downstream. So death of tissue due to lack of blood is called gangrene. There's dry gangrene when there's no infection involved and it's just lack of blood and oxygen that kills the tissue; it's called wet gangrene when there's an active infection along with the compromised blood supply.

Q. And do you have a picture of the dry gangrene?

A. I do.

Q. And what is this picture showing?
A. This is the foot of someone with diabetes. You see here the tips of the toes and in this case the entire toe has essentially just died, turned black, and gradually worn -- worn away because of lack of blood supply.
Q. Okay. So we've now talked about atherosclerosis in the big vessels that can impact the heart, the brain and the limbs.
Have we covered the macrovascular side of the problem?
A. Yes.
Q. Okay. Let's go back and take a look at the microvascular side of this.
This is the slide we looked at earlier. But could you focus on the microvascular portion of the slide and describe for us what is involved in microvascular disease?
A. Sure. Macro is you can see with the naked eye. Microvascular disease is disease of the small vessels; the ones you can only see with the microscope. There are three vessel beds we are particularly concerned about in diabetes; the retina, which is the screen in the back of the eye that lets us see; the kidney and the nerves,

especially the nerves of the leg. One thing that's different about micro versus macrovascular disease, not only which vessels are infected, but how typical it is of diabetes. Nondiabetic individuals get macrovascular disease all the time. It's just very accelerated in diabetes.
Microvascular disease really occurs only in people with diabetes. You don't see this kind of damage in people who don't have diabetes. The main reason is that because the bad actor is the high blood sugar causing damage to these vessel beds. When high blood sugar damages the small vessels of the retina, we call that retinopathy. Pathy just means disease, so it's retinopathy -- disease of the retina -- it's diabetic and it's the leading cause of acquired blindness in the United States.
Nephropathy or disease of the kidney due to diabetes. That's the leading cause of kidney failure in the United States, which used to be uniformly fatal before dialysis. Now diabetic nephropathy is the leading cause for Americans to go on hemodialysis.
And neuropathy is disease of the vessels leading to the nerves, especially in the

leg. It turns out to be the leg that's affected because those nerves are the longest. They go from the spinal cord all the way down to the leg. So they're more vulnerable to lack of blood supply, oxygen and nutrients. Neuropathy can first lead to pain in the absence of any sort of pressure. For example, the type of pain that people get with shingles, it's a nerve pain. Very troublesome. Then there also could be sensation loss, which is ironic given they could have pain but also lose a sensation. So the big worry in people with severe diabetic neuropathy is they'll step on a nail and not notice it until the foot's infected. So the sensation loss can be that profound.
And then the sensation loss, the risk of trauma and injury to the leg and the likelihood they may not find infections early when they happen all predispose to serious infection, gangrene and limb loss.
Q. Let's focus on the retinopathy or the blindness part of it first. Let me pull up another slide and can you describe for us what's involved -- some more detail with respect to diabetic retinopathy.

A. Sure. As I mentioned, hyperglycemia or high blood sugar is the culprit here, the small vessels, the microscopic vessels of the retina. If it causes some damage directly, it damages the wall of those vessels so they get, on the one hand leaky, on the other hand blocked. So the retina -- the retina experiences a loss of oxygen. It attempts to compensate by growing out new vessels to bring in blood supply around those blockages. The trouble is that the new vessels are really quite fragile and they don't grow just in places where they should grow, so it creates problems for the eye. It's an adaptation that turns out to be dangerous. A maladaptation.
And so diabetic eye disease, diabetic retinopathy can interrupt vision in a variety of different ways. The leakage of the fluid and the proteins from the vessels, if that leakage occurs over the part of the retina problem that's involved in visual acuity called the fovea, that can lead to blindness. The new vessels grow out; they're very fragile. If they rupture and bleed and the bleeding occurs over the point of visual acuity, over the fovea, you can get blindness from that.

The new vessels don't confine themselves to the retina, the movie screen in the back of the eye; they should. Many of them grow out to the vitreous, which is the jelly-like part of the eye that forms the bulk of the eye. When those vessels grow out to the vitreous, you can have hemorrhage there, so that can just block the light from coming in the back. The new vessels can also tug the retina in such a way that it detaches. And a detached retina can cause blindness. There's also a damage in front of the eye that can lead to buildup of pressure and glaucoma and loss of vision from that route as well.

Q. Do we have a diagram of the eye that illustrates those different processes that you're talking about?

A. We do.

Q. Tell us what this slide shows.

A. Sure. Here's the eyeball. Here's the front of the eye this way, the back of the eye that way and then the brain would be normally back in the back here. Here's the retina, the movie screen in the back of the eye. The light comes in the front, focused by the lens, goes on

the retina, signals picked up rods and cones, those cells we learned about in grade school. They send signals back to the brain and we are able to see.

The retina is the movie screen in the back. The vitreous is the jelly-like substance between the lens and the retina. This section here shows a small part of the retina, and shows all the things that can go haywire. Here's an arterial that's been affected by diabetes. One -- one consequence is that the vessel wall weakens and you get the formation of microaneurysms these little red spots, outpouches of very tiny vessels. They're not dangerous in themselves but they're used by ophthalmologists to detect the early ill effects of diabetes.

Then those vessels, as they get leakier and leakier, they can leak out protein, and this whitish material that we call exudate. They can also rupture and blood can be released into the substance of the retina, a hemorrhage. And then these new vessels grow and they're especially predisposed to hemorrhage, and they can also pull the retina from its moorings and detach it.

Q. Let me interrupt. The sort of orangey color there, that's the retina?

A. Yeah, this is the substance of the retina. Here's the vein going to the retina. Here's the artery. Fresh blood goes out of the artery, comes back in the vein. This orange substance here is the rods and the cones, the part of the retina that lets us sense light and see. And where all these arrows go, there's other stuff in the retina that shouldn't be there. The exudate, the abnormal vessels, microaneurysms and the hemorrhage or the blood in the retina.

Q. So is the problem with exudate, for example, is that a problem where the exudate is sort of covering the rods and the cones and preventing the light from impacting those cells and being detected?

A. Yeah, with hemorrhages and exudate, it can be just physically blocking the light or it can be destruction of the underlying tissue by poisoning the local environment essentially.

Q. With respect to the hemorrhage there, is that also obscuring the cells that pick up the light and send those signals to the brain?

A. Again, the hemorrhage can block the light or be directly toxic to the fragile cells in the immediate neighborhood.

Q. Those little abnormal blood vessels, what's the problem with those? Why do we care about that?

A. That's the adaptation to the lack of blood supply, because the first thing that happens is that these arterials are narrowing in diabetes and the retina is sensing that it's getting less oxygen than it should. It sends out signals to the blood vessels to grow out, as if there aren't enough vessels. Unfortunately, when people reach childhood and young adulthood, let alone adulthood, those new vessels that grow out, they're not like the old ones. They're not as good, they're not really functional, they cause more harm than good, they're small, they're tangly, they're very fragile.

Q. So if they're fragile do they hemorrhage?

A. Yes, these vessels are at the highest risk for hemorrhage. Once this occurs -- once ophthalmologists detect this, they can see this when they look in the back of the eye. Once they

detect this they begin laser therapy to knock out those vessels and sometimes to burn a moat around the diseased area to prevent it from affecting the less of the retina.

Q. Okay. Because if those vessels do bleed, then they obscure the rods and cones?

A. Damage the cells or obscure their contact with light from the outside.

Q. Okay. Let's talk next about diabetic nephropathy, where the kidney gets damaged. Do we have a slide that explains that in more detail?

A. We do.

Q. If I can get this to work.

MR. SUGGS: It's shooting, but it's not --

Okay. I think we went too far. There's one entitled Diabetic Nephropathy I. There we go.

Q. (BY MR. SUGGS) Can you explain to us what's involved with diabetic nephropathy or damage to the kidney?

A. Sure, well, this is the characteristic damage to the filtering part of the kidney. It's called the glomerulus. It's where the blood

supply comes in contact with the structures that lead to the urine. And there's microscopic damage there that causes two problems kind of in parallel with what is happening in the retina. Those vessels become more leaky is one problem. And when those vessels are leaky, the blood loses vital proteins out into the urine that should normally be kept in the body, but are wasted in the urine and come to the outside world.

Keep in mind, the kidneys are constantly filtering our blood on the order of 50 liters a day passing through that filtering system. There should be very, very little protein coming out. Our body works hard to build that protein. We want to keep it in. It's one of the ways that physicians detect diabetic kidney damage by testing the urine for protein.

Q. Can I interrupt for a second. The body needs those proteins and that's the problem with them leaking through?

A. Yes. For example, one of the proteins is albumin, one of the most common proteins in the body, forms the white in egg whites. That's the protein that gives us -- allows the circulation to work as well as it does because we

send blood -- say the heart pumps blood to, say, our legs. It pushes all the nutrients, pushes a lot of the fluid out. And then on the return trip it has to have a way to re-collect the fluid and minerals. The only sort of pressure dragging the fluid and minerals back is called osmotic pressure, it's because the protein concentration in the blood of albumin is maintained high enough that it actually sucks that fluid back in. When albumin levels drop, and the blood goes to the leg, the fluid gets pushed out and never comes back and is one of the causes of leg swelling and fluid retention in the legs. That happens in other parts of the body, for example, the chest and it causes shortness of breath and trouble there.

Q. Okay. I interrupted you. Can you go back and explain what you mean by less filtering?

A. So one problem is the leakiness. The other problem is sort of not leaky enough. One way to think about this is using a coffee filter to make coffee. You don't want the filter to be leaky and let the coffee grounds go into the pot. You don't want it that leaky. On the other hand, if the filter doesn't work, if it was made of

linoleum, you wouldn't be able to make coffee because it needs to filter to a certain extent. You need a filter that works just right.

Diabetes creates two problems for the kidney. It makes parts of it more leaky and it makes part of it not leaky enough. So the overall amount of filtering that goes on decreases. This is the bigger problem, because when there's not enough filtering, the waste products accumulate in the blood; acids, other toxins, waste products formed by the normal metabolism of all the cells in the body. When those waste products build up, they can cause illness and if untreated, before we had dialysis, would lead to death.

Q. And you note there early damage shows in blood and urine tests; is that correct?

A. Yeah, current recommendations for the care of people with diabetes include frequent blood and urine testing. Some of that is to check the sugar but some of that is also to check on the kidney. We can -- in the urine we can measure the leakiness of the kidney, how much protein there is. And then in the blood we can measure how waste products are breaking up. We

measure a substance called creatinine, a waste product formed by muscle. When it's normally filtered the level should be low in the blood. And as the filtering system of the kidney begins to deteriorate, we'll start to see levels of this molecule go up. It's not dangerous in itself but it stands for the collection of other waste products that signal trouble.

Q. Okay. I think we had another slide here that further discusses this but I think you may have covered some of the items in there. Let me see if I can pull it up. Okay. Did I do that or did you do that?

Okay. Could you tell us what's involved in this slide, what the later problems are?

A. Sure. Well, early on, kidney disease is pretty asymptomatic. People don't know that they have it and that's why physicians have to check the urine and the blood to get early signs. You wouldn't know you have it at all. One of the reasons we have two kidneys; there's a bit of redundancy there. You can take out a whole kidney. You could lose half your kidney function and not notice it. That's the basis for kidney

transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems are more serious than just abnormalities on tests. Now fluid begins to accumulate in the legs and chest, as I mentioned a moment ago. People don't feel right. Fatigue, loss of appetite, nausea. And then waste products begin to accumulate in the blood, especially acids. Our body generates a lot of acids in the course of normal metabolism. If they don't come out in the kidney, they build up in the blood. The pH drops and that's incompatible with life. The thing that keeps people alive, once they develop full-blown kidney failure, is either transplantation or hemodialysis. And diabetes is the leading cause of kidney failure and the need to go on dialysis in the United States.

Q. Okay. And there is, I think, one other element of microvascular disease that we have yet to talk about and that's diabetic neuropathy; is that right?

A. That's right.

Q. Okay. Let me go to that.

If I can. There we go.

MR. SUGGS: Did I do that or did you?

A SPEAKER: You did it.

Q. (BY MR. SUGGS) Very good. Can you explain to us what's involved in diabetic neuropathy?

A. Sure. Neuropathy is damage to the nerves, and as I mentioned a moment ago, that occurs most commonly in the feet and the legs, primarily because those nerve cells are longest -- longest ones in the body. Most vulnerable. And when there's damage to the vessels that provide nutrition to those small nerves, you get a variety of different problems. You can get paresthesias, this is numbness and tingling, pins and needles feeling or you can get chronic pain, shingles-like pain in the leg.

By the same token there can be numbness or even complete loss of sensation, a circumstance where someone could step on a tack or a nail and not know it. That creates a big risk of undetected injury and in fact, one of the directions we give to patients with severe diabetic neuropathy is don't rely on sensation to tell you what's happening with a foot. Make sure

every night before you go to bed you look at the bottom of your foot. If you can't get your leg up high enough, use a mirror, and if you still can't see, have someone else in the family look at the bottom of your feet and make sure there's not something sticking in it or some infection there. You get an increased risk of infection. And that infection can be much more serious than a typical skin infection in a nondiabetic person. Not only do they have the nerve injury that's leading to the injury, but -- leading to the injury and also leading perhaps to delayed detection of an infection, but most of them also have some degree of peripheral arterial disease, the atherosclerosis in the arteries that lead to the leg so they also have compromised nutrition, decreased blood flow and oxygen. That's a recipe for some very serious infection and an extreme would be gangrene of the leg, an infection so severe that it's incompatible with life and the toe or foot or leg has to be amputated. And diabetes remains the leading cause of nontraumatic leg amputation in the United States.

Q. And do we have a picture of a foot showing the problem with diabetic neuropathy?

A. Yes, we do. This is an example of what can happen in the foot of someone with diabetes where they've lost sensation, and they can't sense that these things are going on. So, in most of us we'd have a callous or an abrasion, we'd pick it up right away. We'd ease up on the foot; we'd put a Band-Aid on it; we'd change shoes. They can have pretty serious damage and not notice it and it can progress from this kind of ulceration to this kind of ulceration, down deep penetrating down to the bones underneath. When this happens, this is often a sign that not only the superficial skin been infected, but the deep parts of the skin and even the bone underneath.

MR. SUGGS: Very good. Your Honor, I don't know what time you usually take your break.

THE COURT: This would be about it if it's a convenient time to break.

MR. SUGGS: This would be a perfect time. We're about ready to switch gears here.

THE COURT: Ladies and gentlemen of the jury, we're going to take our first morning break. It will be about 15 minutes. Again, I'll

remind you, please don't discuss this case among yourselves or let anyone discuss it with you. Please try to keep an open mind until you hear all the evidence in this case.

We'll be in recess for about 15 minutes.

(Break.)

THE COURT: And we're back on the record and all members of the jury are present.

Mr. Suggs.

Q. (BY MR. SUGGS) Thank you, Your Honor. Dr. Brancati, I want to shift gears now and talk about what epidemiologists do to determine what factors are associated with the development of diabetes. In the field of epidemiology what is the definition of the term association?

A. We say A is associated with B when they go together in studies of patterns of disease and population. So, for example, we might say cigarette smoking is associated with chronic bronchitis, because if we do a survey and ask people about how much they smoke and we also ask them whether or not they have a chronic cough or they are told by a physician they have chronic bronchitis, and we see that bronchitis is more

chronic in the smokers than the nonsmokers, then we say chronic bronchitis is associated with smoking.

Q. Does association necessarily means causation?

A. Causation means when you know that A leads directly to B, or A is an important contributing factor to B, but often A and B can go together for reasons other than causation.

For example, gray hair predicts the risk of heart disease and stroke. It does because it's associated with age, but there's an unmistakeable connection there. My kids when they were little understood that and used to try to scrub the gray out of my beard because they thought that would protect me against getting ill the way they saw their grandparents were ill. That's a mistake. They saw that gray hair was associated with illness, but it's a noncausal relationship. It's explained by other factors.

Q. The field of epidemiology, do you use a term called risk factor?

A. Yeah.

Q. What do you mean by that?

A. Commonly know -- the term risk factor is

used a lot, for example, in cardiovascular disease where we can tick off risk factors for heart attack. For example, high blood pressure is a risk factor for heart attack. High cholesterol is a risk factor for heart attack. The interpretation in that setting is that this is a factor that contributes to the occurrence of the disease and the implication is if we can modify that risk factor, if we can change it, if we can reduce it, then we might be able to prevent the complication. So, high blood pressure is a risk factor for heart disease. That's been pretty well proven for now in 30 years of research and it turns that out if one reduces blood pressure by treating it with drugs, one can help prevent a heart attack.

So it's a term we use in epidemiology when we're identifying a potential culprit for the occurrence of subsequent disease. We do a variety of studies to first see that association and then as that association grows stronger and stronger, that relationship may grow into a risk factor relationship and get to the point where we say, gee, we know enough about it that this is a risk factor we can act on. We

should go after that risk factor as a means to prevent its health consequences.
Q. When epidemiologists use the term risk factor, does that imply that there is some sort of causal relationship?
A. Yeah. I'll say that some of my colleagues disagree about the precise terminology because there's no authority that governs the language specifically, but I'll tell you what I do and what we commonly do at Johns Hopkins is that -- I use the term risk factor when I'm thinking that the relationship is probably causal. I say probably because it's often impossible to prove with 100 percent certainty a causal relationship.
Take the circumstance with cigarette smoking and lung cancer. We have incredibly strong evidence that cigarette smoking leads to lung cancer, but no one has ever done the definitive experiment to prove it with 100 percent certainty. That experiment would be to take thousands of people at risk for lung cancer who don't smoke, flip a coin, randomly assign some of those folks in that group to smoking, others in that group to nonsmoking and then

continue that for 10, 20, 30 years and count up the number of lung cancers in each group. Can't do that. It's not ethical because there's no presumed health benefit to smoking; it's a harmful exposure. So you could never do that kind of randomized control trial. You'd never get 100 percent certainty.
Take another example. Epidemiologists like to study common components of the diet, for example, coffee drinking. I like drinking coffee, so I follow that literature closely. It wouldn't be unethical to do that sort of study if one were interested in the potential relationship between coffee consumption and heart attack, for example. You could conceivably take thousands of people and ethically randomize half to coffee consumption and the other half not. It would just be very difficult to do. It's not an ethical problem, it's a logistical problem. How do you get people who feel completely balanced about coffee consumption or not and take half of them and have them drink it for 10 or 20 years?
So there are some answers that we never get to 100 percent certainty, and that's so

often true that in epidemiology, we often -- a lot of our investigative battle is to get relationships from the point of just a vague association to the point that we say, yeah, this is looking like a risk factor, we have enough information to act on, either at the clinical level in the office or at the public health level in terms of policy.
So there are some answers that we never get to 100 percent certainty, and that's so often true that in epidemiology, we often -- a lot of our investigative battle is to get relationships from the point of just a vague association to the point that we say, yeah, this is looking like a risk factor, we have enough information to act on, either at the clinical level in the office or at the public health level in terms of policy.
Q. And when epidemiologists say that some factor, whether it's a drug or chemical agent or whatever increases the risk of developing a disease, does that imply also that there is a causal relationship?
A. Yeah, it implies that we're definitely thinking there's a causal relationship. Now, for

example, I wouldn't say that gray hair increases the risk of heart attack. I'd say gray hair is a predictor. But when I use the same increases the risk of it, yeah, I'm thinking it's potentially causal. It could always be proved otherwise in a definitive, large-scale study but we rarely get to that point. Often in epidemiology where we're on the track for identifying new risk factors and seeing how strong it is, we're doing studies and looking at evidence to see if we can move that factor from a mere association into the range where we say this is looking like a risk factor.
Q. And how do epidemiologists know if a risk factor is for real as opposed to just some sort of quirky statistical fluke?
A. There are a variety of criteria that we apply were developed in the 1960s, specifically in relation to the study of cigarette smoking. Because there was a lot of disagreement in the '50s and '60s about just how harmful cigarette smoking was. There was no prospect of doing a definitive, randomized, controlled human experiment to determine -- to determine the risk unequivocally. And epidemiologists were doing a lot of work that was observational. Not randomly

assigning people to smoking or not but asking people whether they smoked, how much they smoked, and then looking at patterns of disease. In that setting it was necessary to pool the wisdom of epidemiologists working on that problem and develop a set of criteria that could be used to sort out associations without any likely causal link from risk factor associations where it looked increasingly likely that there was a causal connection.

In that setting it was necessary to pool the wisdom of epidemiologists working on that problem and develop a set of criteria that could be used to sort out associations without any likely causal link from risk factor associations where it looked increasingly likely that there was a causal connection.

Q. And were these criteria that were developed, were they called the Bradford Hill criteria?

A. Yes, Bradford and Hill were two epidemiologists working in the field at that time. And they put forward these criteria and we still use them today. When I quiz Ph.D. students at the Johns Hopkins School of Public Health one

of the common questions we ask is: Can you go through the criteria for causality and apply that to their doctoral thesis to make sure that they understand this kind of bedrock concept.

Q. And are these Bradford Hill criteria ways of sort of looking at or analyzing the evidence that's already there for the purpose of determining whether there's a causal relationship?

A. Yes. Can be used to sift through existing evidence so -- to determine just how strong the evidence is and it also helps to -- helps us to see where the holes are and what the next bit of research might be to plug a hole.

Q. And pull up here on the screen a chart that you prepared entitled Bradford Hill Criteria for Causality. Can you walk us through the different criteria and explain how they were -- how those criteria were used in the context of cigarette smoking where they were originally developed so that we can understand what these criteria are and how epidemiologists use them to determine whether there's a causal relationship?

A. Sure. I'd be delighted.

So one criterion is the strength of

association. When we say strength in epidemiology, we mean what's the answer to the question of how many times more likely is someone with A to get B. Or in this case, using the example of cigarette smoking, how many more times likely is a smoker than a nonsmoker to get a specific complication?

The stronger -- the more -- the greater the number of times or the stronger the relationship, the more likely the relationship is to be causal. So I gave some examples here, the relationship between smoking and lung cancer, extraordinarily -- extraordinarily strong, tenfold risk or higher.

Now, there are nonsmokers who get lung cancer and there are plenty of people who smoke who never get lung cancer. So it's not a lock and key kind of thing. But -- but in looking at patterns of disease in population, the odds are stacked against you if you're a smoker in terms of lung cancer risk. It's a very strong relationship.

Now, not all relationships we look at in epidemiology are that strong. That's among the strongest. In the United States where we

enjoy relatively good health at the individual level and at the public health level, we're often more concerned with more moderate levels of risk. For example, I put a more moderate level of association here that we're also concerned with is, for example, the relationship between cigarette smoking and heart disease. Compared to nonsmokers, cigarette smokers are about 50 percent or 1.5 times more likely to get heart attacks than nonsmokers.

It's nowhere near the level of association -- the strength of association between cigarette smoking and lung cancer but it's still important. It was still one of the rationales for launching a public health campaign to prevent kids from starting smoking, and get adults who do smoking to stop smoking. Not only because would it prevent lung cancer, it would prevent heart disease. And in fact, heart disease is a lot more common than lung cancer. So sometimes as an epidemiologist we're more interested in the moderate relationships if -- the outcome is a common one. There could be more at stake More cases of disease to prevent for the more common outcome than the less common outcome.

Q. The next factor you have there is consistency. What do you mean by that?
A. Consistency has to do with how well we're able to replicate the results in different studies. One -- one gripe I always have here about epidemiology studies is every morning you open the paper, heart is bad, coffee is good; it prevents diabetes. It's bad -- we go back and forth and the epidemiologists argue about it and creates confusion for public health officials. There are many circumstances where we get consistency done in different parts of the country, done in different countries, different populations. The more consistent the signal, the more we say the results are consistent.
Q. The next factor you have listed there is specificity. What does that mean?
A. Specificity has to do with the idea when you see A leading to B. It's not also leading to a whole range of other conditions that really don't have anything else to do with B. The reason that's a problem in terms of causality is we still have a lot to learn about human biology, but we know enough that we can connect the dots between different kinds of conditions.

For example, with cigarette smoking, as experts began to study it, it made sense as the results came in, and it turned out that smoking was a bigger risk factor for cancer of the lip, the mouth, of the airways, of the lung, than it was for cancers of the colon or the pancreas. The degree of exposure to cigarette smoke is much greater in the tissues along the path of the smoke than other tissues. Now, it turns out cigarette smoking is a risk factor for some remote cancers, but it's a much stronger risk factor for the tissues directly exposed to the smoke. That's an element of specificity. You're not seeing that cigarette smoking predicts all sorts of bad outcomes; it's predicting a certain set that makes sense.
Q. And the next factor you have listed there is temporality. What do you mean by that?
A. Temporality is extraordinarily important. Maybe I should have put this up first on the list. But temporality means you have time sequence. If A really causes B, then A has to come before B. You can't have -- you can't have A after B.
So, for example, one of the

strongest associations I ever found in a study was the relationship between doughnut consumption and diabetes. And this was early in my career. I was dying to publish it. It was highly significant and very strong. It turned out that people who had diabetes were much less likely to consume doughnuts, and so it actually looked like doughnuts were protective. As you went from one doughnut to two doughnuts to three doughnuts a week, the prevalence of diabetes went progressively down. So I had a highly statistically significant result, but I knew it was nonsensical.
In that study we asked about diabetes and doughnut consumption at the same point in time, and our interpretation was -- and the reason I never submitted it for peer-review publication is I assumed, oh, yeah, the people with diabetes, they're eating fewer doughnuts. Either their doctor told them to eat fewer doughnuts, or they're eating the doughnuts but they're embarrassed to report it, because we're asking them about it and they know that they shouldn't. So in that case we didn't have temporal sequence between doughnut consumption

and diabetes.
Now, if we had done that study a little differently and asked about doughnut consumption and youth and then diabetes in middle age, we would have had that temporal separation. Then we would have known the doughnuts came before the diabetes. That's the establishment of temporal sequence.
Q. Let me turn to the next slide that we have. And the next factor that you have listed there is biologic gradient. Is that also sometimes referred to as the dose response?
A. Dose response. Yes, we use the term dose response when we're talking about a drug and a biological gradient and other settings. This has to do with the notion that if a little bit of A leads to B, then maybe a bit more of A will lead to a bit more of B, and a lot of A will lead to a lot of B.
So, for example, with cigarette smoking, we know that there's a strong relationship between the number of packs people have smoked and the duration that -- the number of years they've smoked those packs. We multiply them together and get pack years. Someone with

80 pack years of smoking, someone who has smoked two packs a day for 40 years, they're at much higher risk than someone who's just had 10 pack years of smoking and quit. So we know that with cigarette smoking there's a strong biological gradient or a strong dose response. That also adds to the evidence for causality.

Q. The next factor you have listed is plausibility. What does that mean?

A. Plausibility has to do with how biologically likely the relationship seems. Now, we don't know everything about human biology, we're still learning. In fact, I'm always surprised when my laboratory colleagues say, we love it when you epidemiologists come up with relationships we don't fully understand because then we go back to the lab, or we go to our mice or our animals and we do studies and try to find out what that means. But we get grief in epidemiology when we report that A goes with B, but no one was ever thinking about that sort of association before. Comes out of left field; it comes out of the blue; it just doesn't seem that plausible.

So, with smoking and lung cancer,

it was really quite plausible that that kind of damage to the airway could -- could lead ultimately to cancer, especially as we learned more about the way the cells of the airway respond to damage from the toxins and cigarette smoke, it became more and more plausible. Initially, the relationship between cigarette smoking and heart disease didn't seem that plausible. People couldn't see exactly how it hooked up. It was really only years later that we worked out all the mechanisms and found out that smokers have a higher degree of inflammation in the blood, and more likely to clot, have more accelerated atherosclerosis, and we could fit all the pieces together.

Q. And the next factor you have there is coherence.

A. Coherence has to do with how well all the research on a particular relationship fits together. Not just the studies in humans, but also the studies in animals or the historical record of what's been happening with disease patterns over time, or studies at the cellular level or studies at the molecular level. The more all the results point in one direction, the

more coherent the whole body of scientific literature, human and nonhuman, the more we're apt to say, oh, yeah, this looks like a causal relationship.

Q. I think we have two other factors to go through.

One is analogy. If I can get it there. Okay. And what does that refer to?

A. Analogy has to do with what happens when we've already gone down a path. We've already found that -- that A leads to B, and now we're looking at -- at whether -- whether Y leads to B. And it turns out that A and Y are similar in some ways, and then we say, oh, that -- we've -- we've sort of already gone down that path, and so I know a little bit about this relationship. I'm not starting from scratch. I'm not starting flat-footed.

I that know there's already a relationship between an exposure that's similar and the outcome, so that adds to the general evidence. So, for example, researchers did a lot of work on cigarette smoking through -- over a period of decades. As time went by, they started to turn to other elements of tobacco smoke. For

example -- other elements of tobacco, for example, chewing tobacco, smoking cigars or most recently, passive smoking; all exposures related to cigarette smoking. But the fact that we knew so much about cigarette smoking made it a little easier to connect the dots in relation to those -- to those other elements of tobacco exposure, whether active or passive.

And, for example, when the -- when the passive smoking literature was developing, the fact that we already knew that direct exposure to cigarette smoke was highly dangerous made it more likely right up front that passive exposure to other people's smoke might be dangerous, albeit somewhat less so.

Q. And then, finally, I think the last factor in the Bradford-Hill criteria is experiment; is that correct?

A. Yes. Experiment is really the acid test. So a few moments ago I talked about the acid test for proving A causes B, which is a large-scale randomized human experiment where you take thousands of people and follow them for decades and then count the occurrence of complications in the two groups. It's easy to

conceptualize; it's very hard to do.

Sometimes, though, we do have experimental evidence like that. Often the experimental evidence is a little more modest, a little more short-term. For example, there was never the prospect of doing that kind of large, long-term study in cigarette smoking because of the ethical concerns, but there were a number of short-term studies taking healthy nonsmokers, having them smoke for short periods of time in controlled circumstances, in hospital research units, and then looking at short-term effects on their lung function, for example.

Those -- those sorts of experiments could be done and they added to the body of -- of evidence. In other circumstances, it's possible to do -- when it's impossible to do a study that lasts 10 or 20 years, it might be quite feasible to do a study that lasts six or 12 months. In those cases one might not be able to count on having the complication itself, the event itself, for example, lung cancer or serious emphysema leading to death, but one could find upstream abnormalities that are on the pathway to the complication.

For example, they might not have full-blown emphysema that restricts them to bed and oxygen, but they might have chronic bronchitis which is on the way to developing full-blown emphysema. You could test that in the short-term experiment and that would add to the experimental -- that would add to the evidence base in favor of causality.

Q. Dr. Brancati, regarding diabetes, in particular, and leaving aside for a moment the question of whether Zyprexa is involved in diabetes, are there risk factors for diabetes that are well established and accepted in the field of medicine?

A. Yes, there are.

Q. And let me pull up this next slide, Risk Factors for Type 2 Diabetes. Can you very briefly describe for us the risk factors that are on this slide?

A. Sure. I've grouped them into two categories modifiable and nonmodifiable. It's just the jargon we use to mean the factors we can do something about; the factors we can change or modify, and the factors we can't do anything about. The ones we can't do anything about, we

don't fret too much over them, except that we know that they can be used for risk prediction, identifying which group's at highest risk to go after the modifiable factors.

So the nonmodifiable factors for type 2 diabetes that are well established, one is age. As people get older, they're more and more likely to have type 2 diabetes. Type 2 diabetes is unusual in kids and young adults. Can happen. It's happening more in this country, but it's a strong risk factor.

Another factor is race and ethnicity. It turns out in the United States that people of European ancestry, we get a lot of diabetes, but we get a lot less than people of every other ethnic group in the United States. So, African-Americans are at higher risk, Hispanic Americans are at higher risk, Native Americans, Pacific Islanders, Native Alaskans, all of those other ethnic groups are at higher risk than their European counterparts.

The third there is family history. I think that's something we all know, that diabetes runs in families, especially type 2 diabetes. It's always one of the questions we

ask -- that I ask when someone comes in and they're concerned about getting diabetes. I know their age, their race, ethnicity. I also ask them about a history of diabetes in the family. If there's been a lot of it, I worry that they're at high risk.

Q And then over on the right-hand side you have the modifiable risk factors. Am I correct that those are the ones that can be altered by behavioral changes to some extent?

A. That's correct. These are the ones we have a shot at doing something about. So obesity is the single strongest risk factor for type 2 diabetes. The gradient of risk across the full range of obesity, from lean all the way up to morbidly obese, is well over tenfold. So it's like over the full range of the relationship between cigarette smoking and lung cancer. It is the single biggest risk factor. That's why it's been the target in studies aimed at preventing diabetes and preventing diabetic complications.

Q. Dr. Brancati, how much weight gain does it take to significantly increase the risk of diabetes?

A. That's a good question. It depends

exactly where you're starting, so I'll answer that in two ways. In epidemiologic studies that relate -- that relate degree of obesity to subsequent risk of diabetes, the risk relationship is exponential, kind of curved upward, like standing at the base of a mountain and looking up.

In judging how much -- what a bit of extra weight does is a bit like taking a yardstick and laying it down on that upward sloping curve. If you're down at the base and you're kind of on very flat ground and you lay that yardstick down, it won't make much of a difference. You're not going to go up very much for going across the yard. But as you get closer to the base of the mountain or as the weight goes up, you lay down that yardstick, it starts tilting up along the side of the mountain. So when you start a little higher, the same amount of weight gain at a lower base that wouldn't have posed much risk at all can now pose more substantial risk.

Q. Dr. Brancati, are people with severe mental disorders, do they have a higher prevalence of obesity?

A. They do.

Q. With people in that category, if a group of people had weight gain of 25 pounds in a year, what would that do to their increased risk of diabetes?

A. If they're starting overweight or obese, it could pose a substantial additional risk. In some studies that weight gain, even spread out over a period of decades, can be associated with a three, or fourfold increase in the risk of diabetes.

The other way to look at it is in studies of people who are right on the verge of getting diabetes and asking them to lose weight. In those studies even weight loss on the order of 5 percent. So in someone who weighs 200 pounds, that might be just 10 pounds worth of weight loss, even that little bit of weight loss has a big effect on lowering the risk of diabetes over the next four years.

So that's been one of the stories, I think, in the past ten years in this field is that many of us presume that -- that the only hope to reduce the risk of diabetes related to obesity was to get everyone from -- everyone who

was obese down essentially to their lean weight. And a lot of Americans are 20, 30, 40 pounds overweight. The story that has developed over the past ten years is that even smaller amounts of weight loss, bringing someone down only partway to their lean weight, could still have big benefits. By the same token, weight gains in that range could have major harm. Small differences in weight could have a multiplier effect in terms of diabetes risk.

Q. I believe you said in response to my prior question -- one of my prior questions -- that if you took a group of people who tended to be on the heavier side anyway, such as people with severe mental disorders, and they had an increase of 25 pounds, you said that there were some studies that if that weight gain was spread out over a decade or so, it could be on the order of a three or four times increase; is that correct?

A. Yeah. Well --

Q. Let me follow up with what exactly that means.

If there's a 3 or 400 -- pardon me -- three or four times higher risk for that

group of folks getting diabetes, what does that translate to in terms of percentage?

A. Well, threefold higher would be 300 percent higher.

Q. And fourfold would be 40 percent?

A. 400 percent.

Q. And if the weight gain was occurring not over -- with that group was occurring not over decades, but over the course of a year, would that tend to enhance the increased risk or lessen it?

A. It's a good question. We don't know exactly, but you'd have to figure it's at least the same degree of risk, at least the same degree.

Q. Okay. Let's switch gears and talk about Zyprexa in particular.

Are you generally familiar with that drug?

A. Yes.

Q. And what is it?

A. It's a second-generation antipsychotic drug. It was developed to modify chemistry of the brain and treat people with psychosis, people who have severe hallucinations or delusions

related to underlying psychiatric disease.
Q. And do you know whether it was indicated for the treatment of schizophrenics and the acute manic phase of bipolar disorder?
A. Yes, it is.
Q. Are there any peer-reviewed scientific articles addressing the issue of whether Zyprexa and other atypical antipsychotic drugs are associated with an increased risk of diabetes?
A. Yes, very many.
Q. Roughly, how many are there?
A. I reviewed over 100.
Q. Okay. And how was it that you went about collecting those articles for review? Was it something that I gave you or any other lawyer gave you, or how did you go about getting those articles?
A. No, not -- not at all. We got them from a variety of approaches. One thing that we do very commonly in research is go to the web site of the National Library of Medicine that allows us to do very efficient electronic searches. So we could put in terms like antipsychotic drugs or specific names of drugs and then put in terms for diabetes, ask the program to match it, and then

the National Library of Medicine will pull up electronic copies of journals. That's how we got to most of the papers.
I also looked at review articles on the topic and dug back through the bibliographies in those review articles, and then I took notes at conferences given by medical experts and those sorts of things.
Q. You said that that was how "we" got those articles together. Did you have some assistance in collecting articles for review?
A. Yeah. Part -- I did. Part of my approach when I'm asked to draft a report, either this type or other types for the federal government, is for a variety of reasons I ask some of the junior colleagues around me to help. First, it gives them some experience. Second, it allows me to deliver a product that's more complete and -- and more -- and more on time. And in situations like this, I rely on people to pull articles for me, abstract information, do some initial drafting, and then I look at it and make sure it reflects my views before I present it to the outside world.
Q. And is this process that you've

described of collecting the 100 or so scientific articles for review, is that how you conduct those types of reviews during the normal course of your research activities?
A. That's exactly right. At Hopkins we have a very active group that does what's called systematic reviews, where we're charged by the federal government with reviewing the evidence in a particular area in order to write a report that could help physicians or policymakers or insurers set policy, and we use a very similar approach.
Q. Okay. And of these 100 articles that you reviewed, when did they first begin to be published in the scientific literature? Let me back up for a second.
Were these articles that you reviewed, were they in the peer-reviewed type of journals that you described earlier?
A. Yes, peer reviewed.
Q. Did you restrict yourself to peer-reviewed articles?
A. We did, yes.
Q. And why did you restrict yourself to those articles?
A. Those are the higher quality papers.

The peer-reviewed papers, as I mentioned a few minutes ago, are the ones that have been subject to the most scrutiny, candid scrutiny by peers at other institutions. So one of the rules we have in academia is when you write a paper, you can almost always get it published somewhere. You just keep sending it around. Even if your peers think the science is bad, you can find someplace for it because there are plenty of journals out there.
I don't like to rely on those sources when I'm writing a report. We also don't like to publish there because my colleagues at Hopkins will know that we've taken the low road instead of the high road, so the gold standard in the field is the peer-reviewed scientific journals.
Q. Okay. Of those 100 or so peer-reviewed journal articles that you reviewed, when was it that they first began to be published with respect to linking Zyprexa with diabetes?
A. Well, really from the -- you know, mid to late '90s and then through the end of 2006 when I wrote the report.
Q. Okay. And I'd like to talk about the

different types of scientific evidence.
Let me ask you this question:
These articles that you reviewed, do they for the most part report on various types of studies that were done to analyze the question of whether Zyprexa is related with hyperglycemia or diabetes?
A. Yes.
Q. Okay. And I presume there were also some review articles that reviewed the literature as well?
A. Yes.
Q. With respect to those articles that talked about studies that were conducted, would it be fair to say that there were probably several different types of methodologies that can be used to conduct such studies?
A. Yes.
Q. Okay. And do we have a chart here that just sort of lists the different types of studies that were done to address the question of whether Zyprexa is related to diabetes?
A. Yes.
Q. There we go. Sometimes it works, sometimes it doesn't.

This chart's entitled, Types of Scientific Evidence Available to Determine Whether Zyprexa Causes Diabetes, and then we have listed there five different types of -- of studies that were available in this area; is that correct?
A. That's right.
Q. Okay. And can you just briefly describe for us what type of -- what's involved in a case report or a case series?
A. A case report is very much what it sounds like. It's a case that sparked the curiosity or suspicion of an individual physician about an individual patient. They saw something going on with that event that they thought other doctors should know about and they write up that case.
Q. Okay.
A. The case series is a series of those kinds of cases. So, maybe when they saw the first case, they were a little suspicious, but they weren't really moved to write anything up, to take the time to do it. But when they saw the second or the third or the fourth case, they say to themselves, hey, I think there's something

going on here. I really didn't expect it the first time. Now I've seen three or four cases. Now I feel motivated enough to write it up.
Q. And can a peer case report just standing alone ever prove causation?
A. No, it can't. Really, no one study by itself, with the exception of that hypothetical long-term, randomized human experiment, ever nails causality. Case reports and case series more so than most, because they're anecdotal, they're single episodes. But having said that, it's an important part of the scientific literature, because often we never get to the other studies unless there's some suspicion based on the keen observation of physicians, and then there are elements of those studies that can add to their persuasiveness depending on the nature of the case report.
Q. Are those case report -- well, let me ask this: Are there particular types of case reports that can, indeed, provide evidence of causality?
A. The type of case report or case series that can be most suggestive of a potential causal relationship are the ones where there's been a

dechallenge and/or a rechallenge. What do I mean by that? The pharmacologists, my colleagues in that field, people who study drugs for a living, they'll consider the initial use of a drug to be the challenge. Somebody goes on drug X and then they get sick and that's the initial challenge.
Now, the dechallenge is when the drug is withdrawn. So, you give someone a new drug, they develop wheezing and asthma. You take them off the drug. If the wheezing and asthma continues, you say, well, maybe it was the drug that started it, but, gee, I wonder why they still have it now.
You get dechallenge evidence of an association when they felt fine; you give the drug; they get wheezing and asthma; you take the drug off; wheezing and asthma gets better. Now it looks like, gee, maybe it wasn't the drug, because they didn't have it before; they don't have it now; it was only when they were on the drug.
Now, if you really want even greater proof and the physician and the patient are willing, you can try a rechallenge. So they felt fine; put them on the drug, wheezing and

asthma; take them off the drug, wheezing and asthma goes away. Then the physician and the patient say, you know, I'd really like that drug. It was really helping me in other ways. Are we 100 percent certain that it was the drug? You say, okay, let's try a rechallenge. So, start the drug again. If wheezing and asthma comes back, you say, gee, it seems like it's got to be the drug. What else could explain that kind of pattern?

Q. The next type of study is what you call cross-sectional studies. Were there cross-sectional studies relating to this issue of whether Zyprexa causes diabetes?

A. There were.

Q. What's involved in that type of study?

A. A cross-sectional study is like the study of the doughnuts and diabetes I mentioned a little while ago. Those studies are where you take a group of people and you survey them and you see, do they have diabetes now? Are they eating doughnuts now? Do they have diabetes now? Are they taking Zyprexa now?

It's not the optimal study designed for making inferences about causal relationships

for the reason that I mentioned to you before. You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker designs.

Q. Were there case-control studies addressing the issue of whether Zyprexa can cause diabetes?

A. There were. The idea behind a case-control study is that you try to arrive at some temporal sequence. For example, in the diabetes and doughnut example, rather than asking them, how many doughnuts are you eating now, you group people into diabetic or nondiabetic. Then you ask them, how many doughnuts did you used to eat five years ago or ten years ago. Pick a point in time before they would have developed the disease, and then make judgments about the relationship between the risk factor and the outcome.

Q. And were there cohort studies that were available to determine whether Zyprexa causes diabetes as well?

A. There were cohort studies as well. The term comes from actually Roman history. Cohorts in the Roman legion -- Roman warriors were formed into cohorts, groups of about 4- to 500 men who were led by a commander, and the legions would form them up in order to keep track of the troops and be able to do head counts at the end of the day. So you'd send a cohort into battle, you know exactly how many were there. At the end of the day you'd count heads and you'd see where your losses were in what field of battle, and that would help the commander guide war for the next day.

In epidemiologic studies, cohort studies are similar. You form a group of people; you account for every head. Instead of sending them into battle with ancient armies, you send them to do battle with the forces of disease and you count heads if you're looking at mortality or you count cases of disease according to their risk factor status of baseline and then make judgments about risk on that basis.

Q. And, finally, it appears that there were experimental studies that were also available to look at this issue whether Zyprexa causes

diabetes?

A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road.

Q. Okay. Let's take a look at what the results were of your analyses with respect to each of these different categories or types of evidence.

Let's first talk about what the case reports and the case series say with respect to Zyprexa and diabetes. I think we've got a table here -- pardon me -- a slide here that summarizes that. There we go.

Can you describe for us what you found with respect to the case reports regarding the connection between Zyprexa and diabetes?

A. Well, we found many case reports of diabetes occurring in people who use Zyprexa, or hyperglycemia and people with diabetes who went on Zyprexa. There were -- in the majority of cases where there was a dechallenge, there was also an improvement in the hyperglycemia, either

in the normal range or the diabetic range. There was a good bit of dechallenge evidence.

And one of the FDA reports reported ten cases -- ten cases where there was a dechallenge and a rechallenge, and in most of those -- and in most of those cases the hyperglycemia improved after the Zyprexa was taken off and got worse again after the Zyprexa was added back.

Q. And what did you draw from those ten cases?

A. Well, that -- as I mentioned before, the dechallenge/rechallenge type of case report, that's -- that raises my suspicion that there might be a causal relationship.

Q. Okay. And you also note that the FDA reports hundreds of cases of hyperglycemia in people using atypical antipsychotic drugs; is that correct?

A. That's right.

Q. And you were looking at those reports not only in connection with Zyprexa, but also other atypical antipsychotics; is that correct?

A. That's right. In our review we really looked across the whole range of antipsychotic

drugs to put Zyprexa in context.

Q. And the other drugs you have listed there, clozapine, greater than Zyprexa, greater than risperidone, greater than quetiapine; is that correct?

A. That's right. Most of the case reports pertain to clozapine, but Zyprexa was up there nearby. There was a gradient of risks across the different types of atypical antipsychotic drugs.

Q. Okay. Let's look at what you found with respect to cross-sectional studies and the link between Zyprexa and diabetes.

What did you find with respect to those studies? First of all, how many were there and what were the results?

A. We found three cross-sectional studies. The results here were mixed. We didn't expect much and didn't find much.

Q. Why didn't you expect much from this type of study?

A. For the reasons I mentioned before. Cross-sectional studies are subject to these problems of which came first, the chicken or the egg. It's not an optimal design, I think, for

the study, not an optimal scientific design. So I think we found a few of them because colleagues who were studying this decided to do -- a few of them decided on other designs that would be stronger.

Q. Okay. And I think the next category of studies you looked at was case-control studies; is that correct?

A. That's right.

Q. And tell us what you found when you looked at the case-control studies that addressed the issue of whether Zyprexa can cause diabetes or hyperglycemia.

A. These case-control designs involve finding people with diabetes, people without, and then going back in their records to see who was using Zyprexa, who was using another antipsychotic drug, who wasn't using any antipsychotic drug. And if you find more Zyprexa use in the people -- more prior Zyprexa use in the people with diabetes, the cases, then the people without diabetes, the controls, then you surmise, gee, Zyprexa looks like it was a risk factor for developing diabetes.

And in four of the five studies we

found an increased risk of diabetes in connection with the use of atypical antipsychotic drugs, and Zyprexa was one of the leading factors. And in one study they were able to show a gradient, again with clozapine, the oldest of the atypical antipsychotics on top. In this case, Zyprexa and risperidone second, and then quetiapine, again, down lower than Zyprexa. So, again, a gradient of risks across different types of antipsychotic drugs.

Q. Okay. And I believe you looked at a number of cohort studies -- pardon me -- as well; is that correct?

A. We did.

Q. And I think the slide that we have for that one shows that there were 17 cohort studies; is that correct?

A. Yeah, there were a lot of cohort studies. This is a good design for looking at risks associated with a drug. The majority of them found associations between antipsychotic drugs and the subsequent risk of diabetes. Some of those had to do with atypicals relative to typical drugs. Some of those had to do with Zyprexa versus other atypical antipsychotics.

Some of them had to do with the effects of Zyprexa in people with established diabetes. Not all of the cohort studies showed significant signal, but the majority did. And consistent with the case reports and the cohort studies, it looked like Zyprexa was among the antipsychotic agents most likely to be associated with the subsequent risk of diabetes.

Q. And you note in your last point there that two studies found increased risk of diabetes in Zyprexa users over risperidone users; is that correct?

A. Yes.

Q. Does that mean the risk was higher for Zyprexa users --

A. Than risperidone, yes.

Q. Okay. Were there also some experimental studies that addressed this issue?

A. There were.

Q. Pulling up the next slide. Can you describe the experimental studies and what they showed?

A. Sure. Well, again, keep in mind that there's never been a really large, long-term study comparing all the antipsychotic agents in

regards to diabetes and other types of related outcomes like heart disease or so on. So the experimental evidence we have is from shorter-term studies. The shorter term just because they're easier to do, easier to approve people into, cheaper to do. You get answers faster, so the short-term studies always come before the long-term studies.

And most of the short-term studies you see that exposure to atypical antipsychotic drugs, in general, clozapine and Zyprexa in particular are associated with increases in blood sugar. And then the most persuasive evidence comes from a study nicknamed CATIE, Clinical Antipsychotic Effectiveness Trial. This was the largest trial of its kind. It went on for months, and it compared specifically different antipsychotic drugs head to head, which typically isn't done.

You might think that we have a lot of evidence that way with diseases where there are many drugs, but the FDA rarely requires us to do that. So often we have one drug versus placebo, or one drug versus another, or a handful of drugs. It's often hard to come by this kind

of evidence where you have a variety of widely-used drugs in the same trial compared head to head. And in CATIE, Zyprexa was associated with weight gain and with increase in blood glucose measured indirectly through this entity called hemoglobin A1C.

Q. I think we're probably going to be hearing more about that term as we go through the trial. Can we take a bit of time here and explain to the jury just what's involved in that hemoglobin A1C test and how it measures blood glucose?

A. Sure. To explain that, let me take you back to the early 1980s when I was in medical school and I was taught to take care of people with diabetes. In those days, before we had this A1C assay, to determine how someone was doing in terms of their blood sugar level, we had to rely on blood tests, venapuncture of the arm and sending that off to a lab. A little uncomfortable, a little cumbersome. Or we'd check the urine with strips and see how much glucose was spilling over in the urine.

These weren't the best tests because, think about it, we were trying to treat

people with diabetes, bringing them back every two or three months in the office, and then our judgment about their control would be staked on a single blood test. And if it came back high -- if it came back high, inevitably patients would say, Doc, I'm generally doing well. Oh, last night I had a big sandwich before I went to bed. That's why my sugar is high today. It was a momentary indiscretion. Don't advance my medicines, not necessary because, in general, I'm behaving. This was just an aberration. It was very hard to manage people's diabetes because both doctors and patients wanted to imagine the best, but the data wasn't the best because blood sugar varies so much from the morning until after breakfast to after lunch. We were always treating a moving target.

An alternative is to get very frequent blood tests done. Send someone home with a meter and check their blood tests all the time with finger picks or bring them back to the office and get multiple readings. Even then, even if you get four or five readings a day, that's a lot. That's a big burden. You're only getting four or five readings and an average of

that.
That's why the A1C was developed. This is a test that relies on an interesting and incidental biochemical fact, and that is that blood sugar tends to bind to the hemoglobin molecule. Hemoglobin may sound vaguely familiar to you. If it does, it's because it's one of the most common proteins in the body. It's what carries oxygen in blood. Actually the iron in blood is bound to hemoglobin. That's what gives blood its red color. So there's a lot of it, and it circulated all throughout the body.
Now, what does hemoglobin have to do with diabetes or sugar? Really, nothing, except there's so much of it acts like an incidental -- an accidental bystander, actually a little bit like a sponge and it absorbs a little bit of blood sugar, and a single sugar molecule combined on to one sticky end of a hemoglobin.
In people without diabetes, about 5 percent of all the hemoglobin molecules circulating in the blood have a sugar attached. We say their hemoglobin A1C is 5 percent. That's at normal levels of blood sugar. As the blood sugar rises, that percentage goes up. It goes

from 5 to 6 percent to 7 percent, can go to 11 or 12 percent. Doctors compare notes, the highest A1C they've ever seen. Could be 13 or 14 percent. Each 1 percentage of A1C represents about 35 milligrams per deciliter of glucose.
The great thing about A1C and the reason it's so widely used in practice now is that it's really impervious to what happened the night before or what happened the morning of the test or even what happened the week before. It ends up being a time average of blood sugars over the life of the red blood cell. Red blood cells circulate for about three months, so this is a biological average of blood sugar over a period of three months. So it's a much more stable measurement than blood sugar, much more reliable, and you can draw it in the morning after a fast. You can draw it in the afternoon after a Big Mac. The Big Mac won't affect it.
So it's very useful in studies, like the studies done of antipsychotic drugs because people who don't do -- researchers who don't do diabetes research tend not to fuss about the time of day they bring patients back for their study tests. In fact, it's more convenient

to let people come whenever they want, 8:00 in the morning, 2:00 in the afternoon, 6:00 at night. It's easier to do that. Many studies outside the diabetes and heart disease world do that. They let people come back any time of day.
That creates a little bit of a problem when you go back and try to figure out if your medication is causing problems in terms of blood sugar, because the blood sugar varies so much during the day you introduce a lot of noise. That's one of the inherent problems in the literature around blood sugar and antipsychotic drugs. There's a lot of noise introduced by the fact that in many of the studies participants came back at different times of day. After a meal the blood sugar can be a lot higher.
The CATIE investigator showed a lot of foresight by building in the A1C. They were thinking about the hypothesis that Zyprexa and other atypical antipsychotic drugs might provoke hyperglycemia. They measured blood sugar, but predictably they got a lot of noise in that measurement. They also built in the A1C so they can get a precise measurement. We don't have this in many studies of hyperglycemia, but in one

of the best and biggest studies we do.
And Zyprexa raised hemoglobin A1C about .4 percent. One percent is about 35 milligrams per deciliter; .4 percent is around 15 or 17 milligrams per deciliter. It turns out it actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result.
Q. Just to make sure I understand this.
The CATIE study which used that hemoglobin A1C test found that Zyprexa users had higher levels of blood glucose as compared to risperidone users and for perphenazine users and ziprasidone; is that correct?
A. Yes.
Q. In your view, was the use of that hemoglobin A1C test in the CATIE study, was that a particularly appropriate methodology to address this issue of whether Zyprexa can cause hyperglycemia?
A. I think it was -- it was a smart idea, because the blood sugar levels can vary quite a bit especially if people come back for visits at different times of day. If you get people back at exactly the right time and you do a fasting

blood glucose, often that shows more of a signal than the A1C because it takes persistently high glucoses to budge an A1C. But if -- it's a good hedge against the noise in the -- just the simple glucose measurement because it's a nice time average.

Q. And is the trade name for risperidone Risperdal?

A. Yes.

Q. Is the trade name for ziprasidone Geodon?

A. Yes.

Q. Do you know the trade name for perphenazine?

A. I forget offhand.

Q. I did too. I was hoping you would know.

We talked earlier about the Bradford-Hill criteria and how epidemiologists use those criteria to evaluate whether a relationship is causal. You've now told us the findings -- or summarized the findings from these various different types of evidence contained in these different types of studies.

What I'd like for you to do now for

us, Doctor, is I'm going to pull back up the Bradford-Hill slide listing those criteria, and I'd like you to tell the jury whether the evidence that you've seen, the review of 100 articles, using the Bradford-Hill criteria demonstrates causality.

Will you do that for us?

A Sure.

THE COURT: Before you do that, Mr. Suggs. Doctor, when was the CATIE study done, and when was it published?

THE WITNESS: CATIE was 2004, I think. Let me double-check. Sorry, I didn't get the reference section in the back of my report.

MR. SUGGS: It's not included in the copy there? I apologize, Your Honor. His report had a list of citations at the back and apparently the copy that we have here doesn't have that.

THE COURT: Okay.

MR. ALLEN: I have it in my hotel room if you want me to go get it.

MR. SUGGS: We'll get the information to you, sir.

THE COURT: Thank you.

Q. (BY MR. SUGGS) Doctor, could you walk us through the Bradford-Hill criteria in connection with the studies that you've reviewed and tell us whether the scientific evidence that you've reviewed satisfies the Bradford-Hill criteria and demonstrates that Zyprexa can cause diabetes.

A. Sure. Well, I think there's pretty good evidence in all of these domains with the possible exception -- with the likely exception of biological gradient. Let me start at the top and go through the other domains.

So, first is strength, and the relative risks, the degree to which Zyprexa appears to multiply the risk of diabetes. It is quite variable. It ranges from lows in the 1.5 to 2 range, all the way up to the 4 or 5-fold range depending on the study design. One nice way to settle that would be in experimental studies, but none of the experimental studies have been taken all the way out to the occurrence of diabetes, so we can quantify the effect on blood sugar A1C; we can't really quantify the long-term effects on diabetes risk. But I think the strength is in the moderate range.

Consistency; there's a lot of that in my opinion. I see that same sort of gradient of risk in the case reports, in the -- include the dechallenge and rechallenge component. I see the consistency in the case-control studies, the cohort studies, and the experimental studies even though not taken all the way to the occurrence of diabetes. It's consistent because you see substantial increases in blood sugar. That's exactly what I'd expect for a drug that leads to the occurrence of diabetes. So I think the consistency is good.

Specificity is pretty good, too. We didn't come across a lot of reports of Zyprexa in association with a whole wide array of adverse effects that would make you think, gee, it's not the drug, it's the people who take the drug. We were focused on diabetes and obesity. What we came across was also some data on cholesterol and blood lipids that went in a similar direction. That made a lot of sense because that's tied up with metabolism and obesity. So -- so I thought the specificity was good.

Temporality; we definitely have from a case control and the cohort studies and

certainly the experimental studies where the exposure to Zyprexa was specifically manipulated as part of the science.

Biological gradient, I lead off saying I didn't really see great evidence there in terms of duration of dose or the amount of Zyprexa taken, so I think that's a weak spot.

Plausibility; I'd say -- we didn't go after animal studies, but the references we saw in the reviews, I think, were consistent enough that the results were biologically plausible. And I think the biggest factor here for me was the very strong association between Zyprexa and substantial weight gain. Weight gain, as I said a few moments ago, is the leading risk factor, the single strongest risk factor for the occurrence of type 2 diabetes.

I could believe that a drug could lead to type 2 diabetes without leading to obesity, but a drug that leads to obesity, right off the bat I have to say, oh, this could be a drug where one of the consequences would be increased risk of type 2 diabetes, so it makes those relationships quite plausible.

Q. Can I pause there and show another slide

from your report that shows the weight change after ten weeks with various drugs and put that in the context with this -- with this issue of plausibility.

Can you describe for us what this chart shows?

A. These are results from a meta analysis published in 1999 by Dr. Allison and colleagues. A meta analysis is one of the techniques that we use when we're doing a very systematic rigorous review of the published literature where we not only sift through the literature and form an opinion, but we actually go through the data in the published studies and add it together, pool it, take weighted averages more or less with bigger studies and better done studies counting more than the smaller studies and the weaker studies.

And the goal is to come up with a quantitative estimate of risk. In a way, that goes beyond merely just looking at the studies and saying positive or negative, and there were more positive studies than negative, so I think there's a relationship.

And when Allison and colleagues did

that -- Allison and colleagues in 1999 asked the question of how weight changes in the presence of antipsychotic drug use. They synthesized the literature up to that point. They did this weighted average that I described. The weighted average is along the Y axis here. The dot represents their best estimate of the pooled average weight gain.

These bars represent something called 95 percent confidence intervals. The bigger the bars, the more blurry the dot, the less certain we are of it. But once you go beyond -- as long as you're within these bars, you're pretty certain you're looking at the -- the statistically accurate effects. So smaller bars means more precise measurement. So they looked at the literature, then they looked at what happened to body weight in people with psychotic disorders --

Q. This was just over ten weeks, correct?

A. Just over ten weeks. What happened to body weight over ten weeks according to the different antipsychotic drugs used. Here's Haloperidol. It's an old-fashioned first-generation drug. Here's placebo, so it's

something that's not effective at all. And, again, you know, as we saw before, olanzapine and clozapine up high here in terms of weight gain, and olanzapine up in the range of a 4 kilogram weight gain. A kilo is about 2.2 pounds, so this was on the order of eight or nine pounds of weight gain in ten weeks.

Q. Is that a large amount of weight gain in that short a period of time in your opinion?

A. Sure. That's a lot to gain in a short period, because if you play that out over a year, five times that, 40 pounds in a year. That's a lot.

Q. And it shows that olanzapine and clozapine are at the highest end over there on the right in terms of weight gain of all those other drugs; is that correct?

A. That's correct.

Q. When you were analyzing the data in the studies in terms of the risk for diabetes, where did olanzapine and clozapine stand on the scale there?

A. Right here. Right at the upper end of the scale. That's part of why the relationship between olanzapine and Zyprexa was so plausible

in my opinion that we -- we already knew it was a strong risk factor for weight gain. Weight gain is the leading risk factor for type 2 diabetes, so one can connect the dots.

Q. Let me go back to the Bradford-Hill table, because there were a couple of other criteria there that you haven't addressed yet with respect to these studies that were targeted, looking at the relationship of Zyprexa and diabetes. I think we left off with plausibility.

Can you tell us whether those studies that you looked at also met the criteria of coherence?

A. Yeah, I think the literature in this field is pretty coherent. It's not only the full range of human studies that I mentioned, but also congruence with data from animal studies, animals exposed to Zyprexa that gain weight and develop similar metabolic disorders. The sense in the field is that there's pretty coherent evidence across the board.

Q. And how about the issue -- or the criteria, rather, of analogy? Does the data fit and fulfill that criteria as well?

A. Remember, analogy has to do with when I

was talking about cigarette smoking. Gee, we know cigarette smoking is bad. It stands to reason that passive smoking might be bad. Second-hand smoke might be bad, because we know that smoke does damage.

In this instance, clozapine had been on the market before Zyprexa. Clozapine had other problems with its use, but was known to be associated with substantial weight gain, and as we found in our review, was also a risk factor for diabetes. Clozapine and olanzapine are biochemically related, so it made sense that if clozapine had these problems, olanzapine might as well.

Q. And you say that clozapine and Zyprexa were chemically related. What -- what do you mean by that? Their structure? The molecule?

A. Similar molecular structure.

Q. Okay. And in the field of medicine, is it often the case that molecules with similar structure have similar properties in terms of how they affect the body?

A. Exactly.

MR. KANTRA: Your Honor, we've been quite lenient to Mr. Suggs throughout in terms of

leading questions. I just raise that as an objection.

THE COURT: He's an expert witness and I generally allow a certain amount of latitude with that. Mr. Suggs, if you could keep it down to more of a minimum, but I'll give him some latitude with an expert witness as I will Lilly.

MR. KANTRA: Sure. Thank you, sir.

Q. (BY MR. SUGGS) Dr. Brancati, with respect to the chemical properties or the molecular properties of a drug, what significance do you see when -- when different drugs with similar chemical properties or similar chemical structures, what -- strike that. Let me start over.

What's the significance of similar chemical properties, Dr. Brancati?

A. Well, you know, as I said before, I'm not a pharmacologist or an organic chemist, but my understanding was that from reviewing this literature is Lilly made a great advance in developing olanzapine or Zyprexa, because clozapine was a very effective antipsychotic drug, but was associated with a horrible and

unpredictable complication called agranular cytosis.

So part of the idea back in the development of the drug, as I understand it, was to come up with a similar drug, a drug that would be similarly effective in terms of treating psychosis, which is a terrible condition, but would lack this horrible side effect of agranular cytosis. My understanding from looking back is that Lilly had a big success when they did that. They came up with a similar drug that lacked this side effect, but having said that, looking back, when you make two drugs that are biochemically similar, you know that they'll be a little different, and these two drugs did differ in terms of the risk of agranular cytosis, but that they're apt to be similar in other ways.

Q. Thanks. Did the studies that you looked at also satisfy the criteria for experiment?

A. Yes, they did. Some of the studies were experimental. And a few minutes ago I mentioned the CATIE study, C-A-T-I-E, which I found very compelling. I thought it was the best of breed in terms of those studies.

But having said that, we -- we

looked at the evidence and did not find the large-scale, long-term randomized human experiment that would be the absolute, positive gold standard that would -- that would settle all the questions. Short of that, results are -- you know, interpretations are always a little tentative, but that's the nature of clinical research. We rarely have that kind of definitive evidence.

Q. Thank you, Dr. Brancati.

We've talked about some of your opinions. I want to make sure that we have a very clear record just as what your opinions are. So I'm going to ask you a series of questions about your opinions.

Do you have an opinion, Dr. Brancati, as to whether Zyprexa use increases the risk of developing type 2 diabetes compared to people who do not use Zyprexa?

A. I do. I think Zyprexa increases the risk of type 2 diabetes compared to nonusers.

Q. Do you have an opinion as to whether Zyprexa use increases the risk of developing type 2 diabetes compared to people with severe mental illness who use antipsychotic drugs other than

Zyprexa?

A. I do, especially in regards to certain antipsychotic drugs. So in the evidence that I showed you, olanzapine or Zyprexa look similar to clozapine. In some instances clozapine looked worse, but there were other atypical antipsychotic drugs that look safer in terms of diabetes risk than Zyprexa.

Q. In those prior questions I was asking whether Zyprexa increases the risk. I want to use a little bit different phrasing now.

Do you have an opinion as to whether Zyprexa is a substantial contributing factor in causing diabetes?

A. I do think it is, yes.

Q. Okay. And do you have an opinion as to whether the risk of diabetes associated with Zyprexa parallels the risk of weight gain?

A. Yes, it definitely seems to parallel the risk of weight gain.

Q. Let me be more specific than that.

Do you believe that the risk of Zyprexa causing diabetes is greater than for other atypical antipsychotics other than clozapine?

A. Other than -- other than clozapine, yes. It looks like the risk of weight gain and the risk of diabetes and hyperglycemia is higher for Zyprexa than some other antipsychotic agent.

Q. And, Dr. Brancati, are you the only one who has concluded that the bulk of the scientific evidence demonstrate that Zyprexa increases the risk of hyperglycemia and diabetes?

A. No. There are many other experts in the field who share that same opinion and, in fact, there was a consensus conference convened by many of the leading professional societies with interest in psychotic disease and in diabetes that published a Consensus Statement that expressed a very similar sentiment.

Q. And I'm going to pull up what's been previously marked as Plaintiff's Exhibit 2368, which is already introduced into evidence.

And is this the article that you were talking about, sir, or the consensus development conference you were talking about?

A. Yes, it is.

Q. And the -- am I correct that the conference was -- occurred actually in November of 2003?

A. Yes, that's right.

Q. Okay. And the results or the report to that conference was published in this article that was published in a journal called Diabetes Care in February of 2004; is that correct?

A. That's right.

Q. And are you familiar with the journal Diabetes Care?

A. Yes -- yes, I am. I review for them and I publish there. It's the leading U.S. journal for clinical diabetes research.

Q. Okay. And is it affiliated with the American Diabetes Association?

A. Yes.

Q. Okay. Now, this particular conference that was convened to determine whether there was a consensus on this issue, what were the medical -- were there different medical associations which sponsored this?

A. Yes, there were. There were several. There was the American Diabetes Association. There was the American Psychiatric Association. There was the North American Association for the Study of Obesity, and there was the American Association of Clinical Endocrinology.

Q. And if I could direct your attention to -- I believe it's the bottom of the second page. There's a table. I believe Mr. Allen showed this table, too, in his opening statement.

Could you explain for the jury what it is this table shows?

A. Sure. This table summarizes the deliberations of the consensus panel, which included experts from all those fields about -- about whether and which antipsychotic agents carried the greatest metabolic risk were most likely to cause diabetes. Their interest in the Consensus Statement was to come up with a consensus on risk as a means to guide practice -- as a means to guide practice.

They didn't urge FDA to revoke any of the drugs from the market. Instead, they -- they addressed their concerns to patients and to physicians to tell them -- to kind of give them a head's up and say, we're worried about these associations. We think if you have patients on these particular drugs you should monitor more frequently.

And this was the result of their deliberations. So they list clozapine on top,

olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone down at the bottom. The first column is their judgment about weight gain. Second column, risk for developing diabetes. The third column, worsening lipid profile -- we didn't really talk about today.

For weight gain each plus sign represents the strength of the evidence. So clozapine and olanzapine or Zyprexa are up on top, what I showed you before based on that 1999 meta analysis. Risperidone and quetiapine in the middle. Aripiprazole and ziprasidone associated with very little weight gain down at the bottom.

Then, most pertinent to your question with the second column, risk for diabetes, in the judgment of that consensus -- in the consensus judgment of that group of experts, they judge that both clozapine and olanzapine or Zyprexa were associated with an increased risk of diabetes, in essence, were risk factors for diabetes.

For risperidone and quetiapine they put D, which means discrepant results. They couldn't really tell. They applied the Bradford-Hill criteria. The results were too

mixed. They didn't want to make a call there. But there were some studies that suggested that those drugs might be risk factors, maybe weaker than clozapine or olanzapine, Zyprexa.

And then down at the bottom, aripiprazole and ziprasidone, two agents associated with little weight gain. When they looked at diabetes risk, the consensus panel thought, gee, there's very little additional risk of diabetes in those groups. These sorts of deliberations led the consensus panel to recommend more aggressive screening for diabetes in users of clozapine and Zyprexa.

Q. Now, this consensus panel who reached those conclusions, were they experts in the field of diabetes?

A. Yes, very much so.

Q. And did this consensus conference -- was this just an afternoon thing, or did it take place over the course of several days?

A. It was several days, I believe.

Q. And did this consensus panel of experts, did they review the available scientific literature before the conference?

A. Yeah. They had -- there was a panel

that wrote the consensus and then they received presentations from other experts in the field that attempted to synthesize all the scientific literature for the purpose of the panel.

Q. Was Dr. David Allison one of the presenters there?

A. Yes, he was.

Q. And you're familiar -- we talked about Dr. Allison's study that was published in 1999 showing clozapine and olanzapine having the highest weight gain. Is there a time lag in terms of when an article is published and when the study was -- the data was actually collected?

A. Sure -- well, that 1999 study was a meta analysis, so it included data from previous years synthesized and put together in one place.

Q. But it would have been put together at least in 1999 and available for anyone to read, correct?

A. Sure.

Q. And do you know whether Dr. William Wirshing also presented?

A. He did, yes.

Q. Do you know whether Dr. Allison and Dr. Wirshing are going to be testifying here in

this trial?
A. I believe they are.
Q. Were there also presentations made by FDA representatives at that conference?
A. Yes.
Q. And were there representatives of drug companies who made presentations at that conference?
A. I believe there were, yes.
Q. One of which was Ms. Cavazzoni; is that correct?
A. Yes.
Q. I shouldn't misspeak. It was Dr. Cavazzoni, correct?
A. (Witness nods head.)
THE COURT: You've got to answer out loud.
THE WITNESS: Yes.
Q. (BY MR. SUGGS) After hearing all of that evidence and after reviewing all those papers and after deliberating for three days, this panel of experts essentially came up with these findings; is that correct?
A. That's correct.
Q. If I can direct your attention to some

language that's in this article that talks about the experts' review of the studies and they state: Despite limitations in study design, the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGA's or with other SGA's.
You see that language?
A. Yes.
Q. What does FGA stand for?
A. First-generation antipsychotic.
Q. And SGA stands for second-generation antipsychotic?
A. Correct.
Q. They go on to say: The risk in patients taking risperidone and quetiapine is less clear. Some studies show an increased risk for diabetes, while others do not. The two most recently approved SGA's, aripiprazole and ziprasidone, have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increase risk for diabetes.
Do you see that language, sir?
A. Yes.

Q. And is that consistent with your opinions?
A. Yes.
Q. I'm going to direct your attention now, sir, to the summary section of the article. And at the beginning of that summary, do they talk about a constellation of adverse effects?
A. Yes, they do.
Q. And what are the three that they -- three adverse effects that are discussed in this summary?
A. They mention increased risk for obesity, diabetes and dyslipidemia.
Q. And then down at the bottom in the summary, this panel of experts reported that, quote, These three adverse conditions are closely linked and their preference appears to differ depending on the SGA used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain or diabetes or dyslipidemia, although they have not

been used as extensively as the other agents.
Do you see that language, sir?
A Yes, I do.
Q Is that consistent with your opinions?
A. Yes.
Q. Okay. Now, the dyslipidemia that's referred to there, is that high cholesterol?
A. That's high cholesterol. In the setting of diabetes sometimes it's not so much the high level of the bad level, but the low level of the good cholesterol, the HDL, or high density lipoprotein. So we often use that term dyslipidemia as opposed to hyperlipidemia, which means high LDL, but similar idea.
MR. SUGGS: Your Honor, may I take a moment and confer with my co-counsel?
THE COURT: Please.
MR. SUGGS: Your Honor, does the Court take another break?
THE COURT: I do take another break.
MR. SUGGS: Would it be okay if we took our short one now?
THE COURT: I'd rather if you're close to finishing up, we finished up and then we

took our break.
(Discussion off the record.)
Q. (BY MR. SUGGS) One point Mr. Allen has suggested I go into and I agree. We talked about the number of the cases and the case reports. I believe you said that there were hundreds of reports to FDA of -- of diabetes-related events with respect to Zyprexa; is that correct?
A. That's correct.
Q. Okay. In the -- are doctors required to report adverse events to FDA?
A. In theory, they -- they are. Often -- they don't. Many of them go unreported.
Q. And is it generally regarded in the field of epidemiology and in the area of pharmacovigilance that the number of adverse events reported is only the tip of the iceberg?
A. Yes, it could be only the tip of the iceberg.
Q. I realize it's one of those things you don't know what you don't know, but have there been estimates as to what fraction or percentage of true adverse events ever actually get reported to FDA?
A. In general, that's something I don't

know.
Q. Okay.
MR. SUGGS: Very good. I have no further questions at this time, Your Honor.
THE COURT: Thank you. Ladies and gentlemen of the jury, we're going to take our second break of the morning, and we'll take about a 15-minute break and then we'll begin with the cross-examination of the doctor.
We'll be in recess.
(Jury out.)
(Break.)
THE COURT: We're back on the record and all members of the jury are present.
I'm advised that one of the jurors just asked the clerk whether we're getting out of here at 1:30 today, so this is what I'm going to tell everybody. If -- if the witness, including questions from the jurors, needs five or ten minutes to finish up and be done and that would be the end of it, I'll give the extra five or ten minutes so that we can finish up the witness. If it's going to be more than five or ten minutes, we're going to stop at 1:30 and we'll come back tomorrow with the witness.

I don't know what the cross-examination is going to be like, but I want to be sure we have time if the jurors have any questions as well with this witness. So, like I said, if it's only shortly going past 1:30 so that the witness can be completely done, I'd rather let him get completely done, but I'm not going to go beyond five or ten minutes. If it turns out we need more time than that, we'll just end at 1:30.
Mr. -- and I can't reading my handwriting -- is it Kantra?
MR. KANTRA: Kantra, yes.
MR. SUGGS: Excuse me, Your Honor. I ran off with the witness' copy of his report, if I could just hand it to him.
THE COURT: Please.
MR. SUGGS: I believe Dr. Brancati found the date of the CATIE study that you were asking about.
THE COURT: Okay. Dr. Brancati, what's the date of the CATIE study?
THE WITNESS: September, '05.
THE COURT: Okay. Thank you.
VENIREPERSON: Your Honor, I've got

a brief question, if I could. The study was done in '05, and you asked when it was published?
THE COURT: I asked when it was published, that's correct. And my understanding is that it was published in '05.
THE WITNESS: Yes.
THE COURT: Go ahead.
CROSS-EXAMINATION
Q. (BY MR. KANTRA) Good afternoon, Dr. Brancati.
A. Hi.
Q. You mentioned a study during the course of your testimony called the look-ahead study.
A Yes.
Q I wondered if you could just tell us a little bit more about what that study is designed to do?
A. Sure. It's a randomized-control, a human experiment designed to determine the long-term health benefits of voluntary weight loss in people who have diabetes.
Q. And what is the thinking in terms of what those interventions might accomplish?
A. The thinking is that weight loss might reduce the subsequent risk of heart attack in

people with diabetes.
Q. Any other benefits that might accrue?
A. It's looking at a whole range of possible outcomes. Mortality, other forms of heart disease, peripheral vascular disease.
Q. Okay. Have you consulted at all for FDA?
A. No.
Q. You testified about a -- an atypical antipsychotic other than clozapine -- or other than Zyprexa which is called clozapine, right?
A. Yes.
Q. And you mentioned that they are structurally similar, but also recognize that they are different compounds, right?
A. Yes.
Q. If you were prescribed Zyprexa, you couldn't fill it with clozapine, correct?
A. Correct.
Q. And you mentioned that there was a fatal side effect associated with clozapine, right?
A. Yes.
Q. And you called that agranular cytosis?
A. Yes.
Q. Can you tell the jury what that is?

A. Sure. The blood is made up of many types of cells. Red cells are the ones most familiar to us, but then there are white cells, as well, the ones involved in fighting infection. There are a variety of different flavors of the white blood cells, and some of them are granular sites and they're important in fighting infection. The condition of agranular cytosis is a sudden loss of those cells, and it can be a devastating complication because it can predispose to serious infection.
Q. And ultimately can lead to death?
A. Yes.
Q. Because it's a serious side effect, one of the things that's required is monitoring, correct?
A. Correct.
Q. And the way that they monitor for agranular cytosis is by drawing blood, right?
A. Yes.
Q. In much the same way that you described blood monitoring earlier today, right?
A. Yes.
Q. You told us earlier that you had evaluated the published literature as the basis

for forming your opinions, right?
A. Correct.
Q. I take it from that that you did not consider or rely upon any submissions that Lilly made to FDA in forming your opinions in this matter?
A. That's right, I did not rely on those sources.
Q. So I take it from that, then, that you didn't consider a submission that Lilly made in July of 2000 with respect to an analysis of about 4,000 clinical trial patients; is that right?
A. That's right.
Q. And I would assume, then, from your answer that you would have not considered a submission that Lilly made in May of 2001 that included a second clinical trial analysis that evaluated diabetes risk in patients treated with Zyprexa; is that right?
A. That's right.
Q. And I would assume as well that in March of 2003, the Lilly submission that was made then that evaluated diabetes-related adverse events after 9 million patient exposures, you wouldn't have reviewed that as well?

A. That's correct.
Q. And with respect to a Lilly June, 2003 FDA submission regarding patients with preexisting diabetes and whether their condition worsened on Zyprexa, you wouldn't have reviewed that either?
A. That's right.
Q. I want to take a step back to the May, 2001 submission. And, in particular, I want to ask you a couple of questions around that.
Do you know David Allison?
A. Yes, I do.
Q. Okay. Dr. Allison is a witness for the State of Alaska in this litigation?
A. Yes.
Q. You respect him and the work that he does?
A. Yes.
Q. And you consulted with him in preparing your report in this matter, didn't you?
A. Yes, on one occasion.
Q. You're aware that Lilly invited Dr. Allison in to critique its clinical trials back in the 2000/2001 time frame?
A. It sounds right, but I don't think we

discussed it.
Q. You didn't -- so he didn't tell you what the results of his analysis were?
A. No.
Q. You described diabetes as a condition which is quite prevalent in our society today, right?
A. Yes.
Q. From 1980 through 2005, the number of people with diabetes in this country tripled approximately?
A. Yes.
Q. Sound about right? From about 5 and a half million to more than 16 million?
A. Yes.
Q. In 2005 alone, there were about one and a half million new cases of diabetes? Does that sound right?
A. Yes.
Q. And general estimates for how common diabetes is in the general population of the United States at least is about 7 percent, roughly?
A. Roughly, yes.
Q. Okay. And that means that approximately

20 million people in this country have diabetes?
A. Yes.
Q. That would be about 1 out of every 14 people?
A. Yes.
Q. And of those, about 6 million people are -- have undiagnosed diabetes, right?
A. Yes.
Q. And what that means is that they don't even know that they have diabetes?
A. That's correct.
Q. And that may be due in part to the fact that diabetes in general is a slow-moving condition, right?
A. Yes, I agree.
Q. And as you said, it's not always accompanied by symptoms when it first presents?
A. Correct, yeah.
Q. And that's consistent with the fact that there are often delays in the time that it takes from onset of diabetes to the time of actual diagnosis?
A. That's right.
Q. And you've estimated that that's somewhere between -- can be between 2 and 7

years?
A. Yes.
Q. You're aware that approximately 23 million people have taken Zyprexa?
A. That sounds right, yes.
Q. And since diabetes is a relatively common medical condition, you would expect that just by chance alone you would expect some people to develop diabetes during the course of their treatment with Zyprexa?
A. Yes.
Q. One of the other things that Mr. Suggs asked you about during the course of your testimony was risk factors for diabetes.
A. Yes.
Q. And as someone who is familiar with the disease state of diabetes, you know that there are a number of different risk factors, right?
A. Yes.
Q. And you talked about weight gain as being one of those?
A. Yes.
Q. Obesity, overweight, right?
A. Yes.
Q. But there are also factors, for example,

like physical inactivity, right?
A. Right.
Q. And as you mentioned, family history would be a risk factor for diabetes, right?
A. Yes.
Q. And being over the age of 45 is a risk factor for diabetes?
A. Unfortunately, yes.
Q. And as you said, various ethnic groups in our country have higher risks than others for developing diabetes as well?
A. Yes.
Q. All those would form the rubric of what we are describing as risk factors, right?
A. Correct.
Q. Let's talk for a minute specifically about obesity and overweight. And as you described it, this is probably one of the most well-recognized risk factors for diabetes, isn't it?
A. Yes.
Q. And it's been known for years that that's a risk factor for diabetes; isn't that right?
A. Correct.

Q. Something you learned about as part of your basic medical school training?
A. Exactly, yes.
Q. Doctors frequently tell patients that they need to watch their weight, right?
A. Yes.
Q. And there are extensive efforts, as you mentioned, to educate the public about weight gain as well?
A. Yes.
Q. And as you suggested, the medical community has focused on this question specifically within the context of atypical antipsychotics; isn't that right?
A. Yes.
Q. And Dr. Allison published that chart that you put up on that screen, right?
A. Yes.
Q. And that was published nine years ago, wasn't it?
A. Yes.
Q. Almost 2 out of every 3 adults in the United States are either overweight or obese; isn't that right?
A. Yes.

Q. But two-thirds of the population in the United States is not diabetic, right?
A. That's correct.
Q. In fact, many people who are overweight or obese, as you said, never actually do develop diabetes?
A. Yes. In longitudinal studies where long-term cumulative risks over a lifetime is calculated, it can be as high as 50 or 60 percent. Those are the figures. For example, the lifetime risk of breast cancer is 10 percent for a woman -- or now 12 or 13 percent over a lifetime. For diabetes, it can be as high as 50 or 60 percent over a lifetime.
Q. I understand that, but there are still many people who are obese or overweight but never do develop diabetes, right?
A. Yes.
Q. You also mentioned, I believe, in the list of modifiable risk factors something called insulin resistance, right?
A. Correct.
Q. And as you describe it, insulin resistance means that a person needs to produce more insulin to be able to keep their blood sugar

levels within the normal range, right?
A. Yes.
Q. Does it sound about right that a quarter or 25 percent of the American public has insulin resistance?
A. I'd say roughly, yes.
Q. Again, even though 25 percent of the U.S. population has insulin resistance, 25 percent of the population is not diabetic, right?
A. Correct.
Q. Again, many people who have insulin resistance don't develop diabetes?
A. Correct.
Q. You also described something, I believe, as impaired fasting glucose or impaired glucose tolerance. You recall that?
A. Yes.
Q. Sometimes that's call prediabetes?
A. Yes.
Q. Another term. And the American Diabetes Association recognizes that as a risk factor for diabetes as well, doesn't it?
A. Correct.
Q. Represents a condition where somebody has blood sugar problems, but they haven't

reached a level yet where someone has actually developed diabetes?
A. Exactly.
Q. And there are about 50 million people in this country who have prediabetes; isn't that right?
A. Yes.
Q. And, again, there aren't 50 million people in this country who have diabetes, right?
A. Right.
Q. So many of them don't ultimately go on to develop diabetes?
A. Many -- many do ultimately over a lifespan. But, yes, when you look cross-sectionally, there's only a small fraction that actually have it, and over a period of a year or two or three it's always a small fraction. The point I was making before is that it can accumulate, so many will go on to develop diabetes, but many won't.
Q. Thank you. In your work as a researcher, you've helped to design a number of different epidemiology studies, haven't you?
A. Yes.
Q. And you've designed a number of

different epidemiological studies relating to diabetes?
A. Correct.
Q. And if you were asked to design a study that was intended to look at the question of whether or not an atypical antipsychotic medication or any medication for that matter was leading to the development of diabetes, it would be important for you to know the extent to which risk factors were distributed among the patients who were in the study, wouldn't it?
A. Yes.
Q. And that's because without that sort of information, it would be difficult to make reliable assessments about whether any effects that might be observed were due to effects from the medication or to differences among the people who were actually being treated?
A. Correct.
Q. So if someone were designing this kind of a study that was intended to actually look at the question of whether medication causes diabetes, it would be important to do your best to make sure that the risk factors were as balanced as they could be among the various

treatments; isn't that right?
A. Definitely.
Q. But you're familiar with the fact that within the databases that are used in the context of these epidemiology studies that we've often talked about, that many of the risk factors we've described, whether they be family history or physical inactivity or any number of other things, often those aren't captured in the databases that are used in these epidemiology studies that you've described, right?
A. Yes. And just to amplify, I think you're making a distinction between the observational studies, the cross-sectional, the case-control, the cohort studies that we talked about as opposed to the experimental studies. In the experimental studies, those -- those factors are distributed equally by design. The coin flip or the randomization evens those out. When you say epidemiological studies, you mean the observational ones where we don't assign the use of the drug. We see who uses the drug and who doesn't.
Q. That's exactly my point, right. The databases that are used in these

backward-looking, retrospective epidemiology studies are different from the randomized clinical trials?
A. Let me agree, but also with the footnote, because some, as I described a moment ago, some of the epidemiological studies are prospective. For example, the cohort studies identify individuals at risk for diabetes before they have it and then look forward in the database. I think when you say they look backwards, often even those prospective studies are done with existing databases where all the dust has settled, and it's a matter of the perspective taken by the investigator whether they look forward or backward, but all the dust has already settled.
Q. Within the context of atypical antipsychotics and diabetes, for example, the studies that you reviewed in that context were all studies that were retrospective in design; isn't that right?
A. So the question -- the case reports and the case series are obviously going on in realtime. It's individual --
Q. Individual patients --

A. -- small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the cross-sectional studies, yes, were generally done with existing databases where the dust had settled and it was a matter of the epidemiologist looking for patterns in the existing data.
Q. Are you familiar with a 2007 article by Leslie Sitroen that evaluated risk factors within the context of atypical antipsychotic medications and emergence of diabetes?
A. I didn't prepare for the report anything beyond --
Q. 2006?
A. -- yeah, 2006.
Q. Conventional medical wisdom has it that it takes years for the insulin-resistance associated with weight gain to contribute to the development of defective insulin production, right?
A. Yes.
Q. And defective insulin production at its heart is what diabetes is all about, right?
A. Yes.
Q. And, in fact, you've published an

article that agrees with that proposition; isn't that right?
A. You're referring to the article with -- the article from the precursor study?
Q. This would be your -- actually, why don't we go ahead and just pull that up and make it easier to talk about it. If we could pull up No. 156.
A. Sure. Yes.
Q. And if we can go to the last sentence of the first full paragraph on the -- I believe it's the next-to-last page of the document.
THE COURT: For what it's worth, and I don't know if it's worth very much, my screen isn't coming up.
MR. KANTRA: Sorry?
THE COURT: I said, for what it's worth, my screen with the articles is not coming up.
MR. KANTRA: Oh, is that right? I'm happy to provide a copy.
THE COURT: Never mind.
Q. (BY MR. KANTRA) Sir, do you want a copy of the article, or are you fine looking at the monitor as well?

A. No, I'm good.
Q. If you look at the article, this is an article which is entitled Body Weight Patterns from 20 to 49 Years of Age and Subsequent Risk for Diabetes Mellitus?
A. Yes.
Q. And as you mentioned, this is a Johns Hopkins precursor study, right?
A. Yes.
Q. This is an article where you are the lead author?
A. Yes.
Q. And it was published in a medical journal known as The Archives of Internal Medicine?
A. Yes.
Q. This is considered to be a peer-reviewed article, isn't it?
A. We were very proud of this one.
Q. And you submitted it with the belief that you were making an important contribution that others could learn from?
A. Yes.
Q. And if I could turn your attention to that last paragraph on the last page, and if you

could -- Mike, if you could pull out the if sustained language.
See the sentence at the end there?
A. Yes.
Q. So when I asked you the question of whether or not you had actually published on this issue and written in accordance with the conventional medical wisdom, the answer is that in fact you have published on precisely that point?
A. Yes.
Q. Okay. Now, nearly all of the published articles relating to weight gain and risk of diabetes are -- that you relied upon in forming your opinions are articles that come from long-term studies, right?
A. Correct.
Q. These are articles that -- or studies that look at patients who may be treated for 5, 10, 15, sometimes even 20 years?
A. Yes.
Q. And these are studies in -- these studies that you've relied upon are studies in people who have gained weight for any reason, right?

A. Yes.
Q. They're not limited to patients who are being treated with atypical antipsychotics?
A. No.
Q. In fact, the majority of the studies that you rely upon are not in patients who are being treated with atypical antipsychotics?
A. Correct.
Q. Okay. And as of today, in terms of the available information with respect to weight gain and the development of diabetes, there isn't sufficient information to be able to determine whether or not the insulin resistance associated with weight gain that over time in your belief leads to the development of diabetes can also occur in a matter of months or a shorter course of time, right?
A. The evidence is much stronger for longer periods than it is for very short periods.
Q. Right.
A. Part of the trouble is that most people don't gain weight that fast, so it's been hard to do those studies. Most of the epidemiologic studies with weight gain ask people, what did you weigh at age 18 or 21, looking back from age, you

know, 45 or 50, and look at weight gains over that period. Because, historically, it took that much time to put on weight. And so we know a lot more about sustained -- sustained weight gain.

Part of the rationale of the paper that -- that we published from the Johns Hopkins precursor study is that conventional wisdom was that it was really 10 or 15 years worth of weight gain or 20 that made a difference. We had 30 or 40 years of followup, so we were stretching the importance of weight on the long end. But you're right, you're asking about stretching it on the short end. You know, we know less.

Q. And my point is: You've not done research that's looked at that narrow time frame of weight gain within a small number of months --

A No.

Q -- and whether it leads to the development of diabetes, right?

A. No, I've done the inverse of that which is --

Q. I'm not asking about that, the weight loss. I'm asking specifically about the weight gain piece. You've not done that work?

A. No.

Q. Let me ask you, specifically, about the ADA Consensus Statement that you described earlier.

A. Yes.

Q. You are an active member of the American Diabetes Association, aren't you?

A. Yes, I am.

Q. And you mentioned that you review for Diabetes Care?

A. Yes.

Q. And you're a member of the editorial board of Diabetes Care as well?

A. No.

Q. Have you ever been?

A. I've reviewed for them, but never a member of the board, no.

Q. Okay. But you've done the kind of peer review that you talked about in your direct testimony?

A. I served for two years on the practice guidelines committee of the ADA, which would review guidelines -- ADA-sanctioned guidelines.

Q. Okay. Okay. And those would include screening guidelines for diabetes; is that right?

A. Yes.

Q. Where the risk factors are listed?

A. Yes.

Q. For diabetes?

A. Yes.

Q. And you're familiar with those screening guidelines as they currently exist?

A. I haven't reviewed them specifically to prepare for today, but, yes, generally.

Q. Generally you're familiar with it. And Zyprexa and atypical antipsychotics have never appeared on that list of risk factors in the screening guidelines; isn't that right?

A. Correct.

Q. Are you familiar with what a Consensus Statement reflects? Generally, what it's intended to do?

A. Yes.

Q. And you're familiar with the fact that a Consensus Statement does not represent the official position of the American Diabetes Association?

A. That's correct.

MR. KANTRA: Go ahead and pull up 2000 -- Yale, 2001. And if we could go -- I think it's the fourth page of that document.

Q. (BY MR. KANTRA) While we're getting there, I'm just going to ask you a couple of preliminary questions.

You mentioned when you were talking about the ADA Consensus Statement earlier that there were a number of different entities that appeared and presented at this?

A. Yes.

Q. And one of them was the FDA, right?

A. Yes.

Q. And after the ADA Consensus Statement was published in 2004, there were several people at the FDA who wrote a letter in response to the Consensus Statement, correct?

A. That's right.

Q. And as you can see -- Mike, if you can highlight that one piece of it over there -- those are folks from the Division of Neuropharmacological Drug Products at the FDA, right?

A. Yes.

Q. And you're familiar with the structure of FDA well enough to know that those are people that would have been involved in looking at atypical antipsychotics?

A. Yes.
Q. And in the course of this letter, one of the things that they did was to address the issue that had been raised by the Consensus Statement of the relationship -- whether there was a relationship between the weight gain that occurs while being treated with an atypical antipsychotic and the ultimate development of diabetes, right?
A. Yes.
Q. Okay.
MR. KANTRA: Can you pull up that one paragraph on the bottom left? And if you can go, Mike, to the sentence that begins with "although." And that sentence and the sentence that follows that.
Q. (BY MR. KANTRA) So I want to just -- I want to just take a look at this sentence, and in particular what it says here is that, Although weight gain may be a factor in explaining the increased diabetes risk for SGA's, DNDP -- which is -- that's the part of the FDA that we were just talking about, right?
A. Yes.
Q. -- is not aware of evidence proving that

the treatment emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. And it goes on to say that although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial -- and that's another way of saying the experimental evidence; is that right --
A. Yes.
Q. -- consistent with what you said?
And the epidemiological evidence, which is the cohort studies and the case-control studies that you talked about?
A. Yes.
Q. Have not shown a direct link between these treatment-emergent side effects.
A. Correct.
Q. That's what FDA's view was in 2004?
A. Yes.
Q. When you were talking with Mr. Suggs about your background and what you do --
A. Yes.
Q. -- one of the things that you mentioned was that you teach, right?
A. Yes.

Q. And among other things, what I understand is that you teach students who are learning about epidemiology?
A. Yes.
Q. And one of the things that you do is you help to educate them about this -- how we look at evidence around the issue of causation, right?
A. Yes.
Q. And in helping to teach them about this evidence relating to causation, you help teach them about the same hierarchy of evidence that was up on the screen earlier, don't you?
A. Yes.
Q. And that hierarchy of evidence would run from the case reports that you talked about initially, up through these observational epidemiological studies, to clinical trials or experimental trials at the top?
A. Yes.
Q. Okay. And you had mentioned a couple of times that sometimes work is done with animals to evaluate safety-related issues, right?
A. Correct.
Q. And those types of studies are helpful for identifying ideas for future studies in

humans, right?
A. They could be done for a variety of purposes, but that would be one of them.
Q. Among other reasons?
A. Yes.
Q. And they provide us with ideas, hypotheses, but they need to be confirmed in humans, ultimately, don't they?
A. Yes, yes.
Q. You had testified earlier when you were describing what you called case reports or case series about a particular kind of a case report known as rechallenge cases, right?
A. Yes.
Q. Rechallenge and dechallenge, I think, is the terminology. Again, dechallenge was a situation where a patient is treated with a particular medication, develops an adverse event, the medication is stopped, the adverse event goes away?
A. Yes.
Q. Rechallenge, again, just to make sure we're on the same page, is the same scenario except they're put back on the drug and the adverse event happens again?

A. Correct.
Q. Okay. With respect to these kinds of studies, what we don't have in contrast to the experimental studies or the clinical trials that you've talked about, is what's called a control group, right?
A. That's right.
Q. And so what we don't know with respect to either the dechallenge cases or the rechallenge cases, for that matter, is how many patients were taken off drug having developed it without an improvement, right?
A. Yes.
Q. Similarly, what we don't know is how many patients were put back on drug, but then didn't redevelop the event?
A. Right.
Q. That's just information that we don't have the benefit of?
A. That's right.
Q. And one of the reasons why it's helpful to have information like what I've just described, information about numbers of patients who didn't develop a particular adverse event after dechallenge or rechallenge, is that it

helps us to identify a rate at which something is occurring, right?
A. Correct.
Q. And in identifying what that rate is, it helps us understand whether we're seeing something that is in excess of what we would expect to see or consistent with what we would expect to see?
A. That's right.
Q. With dechallenge and rechallenge cases, we don't always know, many times we don't know, whether, in fact, there have been changes in a patient's lifestyle or medications or medical history that may affect the outcome of it?
A. Could be, yes.
Q. Put differently, perhaps, the reports that -- that are published in the literature or submitted to FDA depend, in part, on the quality and the knowledge and experience of the physician who's actually making the report?
A. Yes.
Q. And how familiar they are with the relevant issues?
A. Yes.
Q. And even within the context of a person

who develops diabetes and then is taken off drug with improvement after that point, there is what is known as a spontaneous remission sometimes, right?
A. Rare.
Q. But it happens?
A. Yes, I -- I've not seen it in my practice, but it could happen.
Q. But you're aware of it?
A. Yes.
Q. It's been reported in the literature?
A. Yes.
Q. And you would agree with me that these individual case reports that we've been talking about are different in kind from the clinical trials that you've described in this -- in this hierarchy of evidence, right?
A. Yes.
Q. And they would be very different in terms of the quality of the evidence from studies that are designed specifically to look at the question of whether there is a mechanism by which a drug can result in causing diabetes?
A. Yes.
Q. If we look back at the case reports that

have been published, what I recall from your testimony is that you said that the first case reports relating to Zyprexa and cases of diabetes were approximately 10 years ago, right?
A. Yes.
Q. You said mid-'90s, I believe?
A. Yes.
Q. And I believe what you told us was that case reports provide a basis, again, for generating ideas, raising awareness of physicians, alerting them to potential issues that they might need to pay attention to?
A. Yes, in general. Occasionally they're so persuasive that they constitute evidence in themselves, for example, a very unusual type of complication that would otherwise rarely or never occur. With diabetes, as you pointed out, it's common enough in everyday practice that it's hard to tell for certain from case reports alone.
Q. You would agree with me that between 1998 when the first case report for Zyprexa was published, and the spring of 2002, the evidence that was available with respect to the issue of whether or not Zyprexa could cause diabetes was limited to case reports?

MR. SUGGS: Object, Your Honor.
THE COURT: What's the basis for the objection?
MR. SUGGS: Objection to the form. He's talking about evidence. What evidence? The publicly-available evidence or including what Lilly knew?
THE COURT: You're referring to the case studies that --
MR. KANTRA: I said the published literature. I believe I said that.
THE COURT: I'll overrule the question. Do you understand the question?
THE WITNESS: Yes, I do.
A. You know, I think we had some of this discussion during the deposition. I didn't structure the report in terms of time sequence, so I took all the data up through the end of 2006 and made judgments in totality. I do recall offhand that by 2002 there was a -- one paper that compiled several hundred case reports that I referenced a few minutes ago verbally with the challenge and the dechallenge and the rechallenge, but I can't --
Q. (BY MR. KANTRA) Just to be clear, just

so you understand what I'm asking --
MR. SUGGS: Your Honor, can we have the witness be allowed to finish his answer?
THE COURT: I don't think -- were you finished or --
THE WITNESS: Yeah.
THE COURT: Okay. Go ahead.
Q. (BY MR. KANTRA) The article or the analysis that you've referenced in regards to those -- those various case reports, separate and apart from an analysis of case reports, if we're talking about cross-sectional studies, cohort studies, those sorts of things within the epidemiological sphere, you're not aware of any epidemiology studies relating to Zyprexa and diabetes that were published before the spring of 2002; isn't that right?
A. That sounds right. No, the vast majority were after that time. I can't recall offhand whether there were any before that time.
Q. Sitting here today, you don't -- you don't remember any?
A. No.
Q. And you've not offered any sort of opinion that the literature as it existed as of

2002 was sufficient to support the conclusion that Zyprexa causes diabetes, right?
A. Right, the published literature which is what I review, yeah.
Q. Published literature, exactly.
Let's talk for a minute about epidemiology studies as you've defined them. The limitations of these kinds of studies, most precisely or perhaps most importantly relate to the issue of randomization, right?
A. I'm sorry? Could you restate that?
Q. Let me phrase it again.
As you think about the difference between what you call these experimental studies or clinical trials --
A. Yes.
Q. -- and these database studies or these case-control cohort studies?
A. Observational epidemiological study.
Q. Observational epidemiological studies. If we're thinking about the contrast between those two things, one of the most important distinctions is the fact that the experimental studies or the clinical trials have the benefit of randomization, whereas the observational

epidemiological studies do not, right?
A. Exactly.
Q. Okay. And randomization refers to the random assignment of patients to different treatment groups, right?
A. That's correct.
Q. And I think you described it as patients are assigned, essentially, on the flip of a coin, right?
A. That's right.
Q. And the benefit of doing it that way, as we talked about earlier, is the fact that you want to make sure that as much as possible people are similarly situated in the two treatment groups so that you can assess whether or not an effect is the result of a medication or something else?
A. That's right.
Q. And without randomization, then, scientists who are studying the risk of whether diabetes occurs in patients on certain medications at higher rates can't be sure of whether they -- the patients were comparable with respect to their baseline risk factors for diabetes?

A. That's right.
Q. Put differently, scientists can't be sure that they're dealing with a level playing field?
A. That's correct.
Q. Okay. And among other things, the absence of randomization in observational epidemiological studies is one of the reasons why an assessment of causation requires a look across all of the data, including the experimental studies, right?
A. Yes.
Q. You wouldn't want to limit yourself to just one bucket of evidence, right?
A. That's right, although, as I pointed out with the smoking example, sometimes experimental data in humans is hard to come by. Sometimes we do put all our eggs in the observational basket. But, in general, yes, when we can, we like to have experimental evidence as well.
Q. And here, certainly you didn't limit your review of the evidence just to the epidemiological studies, right?
A. Right.
Q. You looked beyond that to the

experimental studies as well?
A. Yes.
Q. In the context of these observational epidemiological studies, one of the things that researchers try and do from time to time, or many times try and do, is to go back and try and balance the groups after the fact, right? Adjust for various ways in which the groups might be imbalanced?
A. Yes.
Q. But in terms of being able to adjust for differences in risk factors that might exist between the two groups, this may be evident, but you can only do that if you have the information about the risk factors?
A. That's right.
Q. Your results are only as good as the database with which you're working?
A. Correct.
Q. In evaluating this question of -- or in -- let me start again.
In looking at the question of diabetes and researching the issue of diabetes, there are a number of different ways in which one can go about measuring diabetes as an outcome;

isn't that right?
A. That's right.
Q. One way to evaluate whether or not diabetes has occurred is to look at various thresholds or cutoff points, right?
A. Cutoff points of glucose you mean?
Q. Right. Exactly.
A. Yes.
Q. So, for example, when you spoke earlier about the way in which diabetes is diagnosed, one of the things you said is that if it's a random blood sugar level above 200 with symptoms, that would support a diagnosis of diabetes?
A. That's right.
Q. Similarly, if you have a fasting blood glucose level that is 126 or higher, that would be another basis for making a diagnosis of diabetes?
A. That's right.
Q. When I say thresholds, I'm referring to those kinds of cut points and, similarly, one could also look at prediabetes as a category of cases, right?
A. Yes.
Q. So there we'd be interested in

identifying patients, for example, if they were fasting, had values between 100 and 125, right?
A. Yes.
Q. And so if we're interested in seeing outcomes, whether it's people with prediabetes or diabetes, one way to evaluate that is to look at these categorical cut points, these significant clinical thresholds?
A. Yes.
Q. Okay. Another way that scientists can go about evaluating whether or not somebody in a particular analysis might have diabetes is to look at the question of whether they're actually being treated with medication for diabetes?
A. That's correct.
Q. So, for example, if someone is being treated with insulin, that might be something that would be of interest?
A. Yes.
Q. Or what they call hypoglycemic medication?
A. Yes.
Q. Something which lowers the blood sugar level?
A. Yes.

Q. That would be another way, an acceptable way, a recognized way of looking at whether or not someone had diabetes?
A. Yes.
Q. And then there's also what is sometimes referred to as a continuous analysis?
A. Yes.
Q. That would be equivalent to what is called sometimes an average change analysis, right?
A. Uh-huh, yes.
Q. Meaning that -- put differently, the question is, on average, how -- how much do patients' blood sugar levels go up while they're on a particular medication?
A. That's right.
Q. And that was one of the things that you talked about with respect to the CATIE study, right?
A. Yes.
Q. One of the things you noted in there was that there were increases in blood glucose levels?
A Yes.
Q And then you talked about the hemoglobin

A1C's a little bit?
A. Yes.
Q. And you recalled that in that study as well they also looked at whether or not there were significant differences in patients who were treated with new antidiabetic medications?
A. Yes.
Q. And by that measurement they didn't actually find a significance difference among the treatment groups?
A. I think that's right, yes.
Q. And all of these three measurements, whether we talk about these clinical thresholds, this categorical analysis they're sometimes called, the measurement using initiation of new antidiabetic medications, or this sort of average change analysis, all three of these give us important and complimentary information, don't they?
A. In general, yes, but your question points to one -- one key consideration. That is, going into a trial -- you rightly pointed out that the experiments give the strongest type of evidence because of their ability to balance factors across different groups. So in that

regard, the human experiments, the trials are at the top of the pyramid.
The trouble is, and I think we see it in the CATIE study, is that trials are hard to mount in large numbers for long periods of time. So frequently evidence we have from experiments or trials is limited in time. Might be only weeks or months. When you go into a study with a time frame of only weeks or months, it may not be reasonable to pin your hypothesis on the development of a condition like diabetes or heart disease. In those settings, even though we look at all three end-points for information, my sense going into the study, just reading about the design before reading about the results, was that the most precise continuous measures would be the most informative.
Q. And that's actually an interesting point, because there are studies, and I believe you mentioned this as well during your direct testimony, that if we look at continuous measures or these average change measures, you're aware that within the context of clinical trials that compare Zyprexa with other atypical antipsychotics, there are studies that compare,

for example, Zyprexa with Geodon in a direct sort of head-to-head comparison.
Are you familiar with those studies?
A. Yes.
Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in these average glucose levels?
A. Especially in some of the shorter-term studies, but, yes.
Q. And, indeed, in studies that went up to six months?
A. Yes.
Q. And you're aware of studies that compared Zyprexa with this newer agent, Abilify, right?
A. Yes.
Q. Which is also call aripiprazole in some of your slides, I believe?
A. Yes.
Q. And you're aware that there as well, there is literature which suggests that the increase in average blood sugar levels is not

significantly different between the two groups, again, over studies that go out to a period of six months?
A. That's correct, and one of the problems with some of those studies that I mentioned before is that to the extent that they use nonfasting glucose, that they mix fasting and nonfasting, it does introduce some noise in those studies. That's part of the reason I spent some time talking about the hemoglobin A1C, because I was impressed that that was an end-point that would be more stable and more impervious to the noise introduced by getting blood sugar measurements different times of the day.
Q. Understood, but if we're working with the data that we have --
A. Yes.
Q. -- it's accurate to state that in those head-to-head studies when we looked at the measurements of glucose disregulation that existed, they didn't find differences there?
A. In some studies, yes, that's right.
Q. In forming your opinions in this matter, you evaluated a couple of studies that are known as clamp studies, didn't you?

A. Yes.
Q. And a clamp study is a study which is, as we talked at the beginning, there are things that are called mechanistic studies, right?
A. Yes.
Q. And those are studies that are done to help evaluate whether there is an explanation by which a particular drug might lead to the development of an outcome like diabetes?
A. Yes.
Q. Right?
And they can measure it in two different ways, maybe more, but at least two that we know of. One is to look at the question of, does administering a drug within a clinical trial or experimental setting lead to a situation where the drug is directly injuring the pancreas such that it can't produce insulin?
A. Yes.
Q. And that is called a hyperglycemic clamp study, isn't it?
A. Yes.
Q. Then there's a second study that can be done as well, and that's a study that looks at this question of insulin resistance that we

talked about earlier?
A. Yes.
Q. And that's sometimes referred to as a euglycemic clamp study, isn't it?
A. Yes.
Q. What's done in those kinds of studies is to ask the question of whether, again, in an experimental kind of setting there was an effect of the drug such that people's insulin resistance actually got worse as a result of taking the drug?
A. Yes.
Q. And you're familiar with the fact that there were two clinical trials that Lilly conducted that looked at those issues?
A. Yes.
Q. And those studies would fall into the bucket of evidence that you described as being experimental, right?
A. Yes.
Q. And the results of those studies, each of them, found that there was no evidence of a direct effect either on insulin production, right, or increasing insulin resistance?
A. I think that's right, and my

recollection was both of those clamp studies, which were well done, were both short-term, I think, with -- two or three weeks or so, if I recall properly.
Q. Done -- done on an acute basis, right?
A. Done on an acute basis. So, I thought those were smart studies to do. Those studies helped convince me that it -- it made it more probable in my opinion that it was the weight gain from Zyprexa that might lead to the increased insulin resistance in diabetes as opposed to an acute toxic effect of the drug on the pancreas or on insulin signaling.
Q. Let me put it slightly differently, which is: Based on your review of the literature in terms of these mechanistic studies, they don't provide support for the idea that the drug causes diabetes by directly entering the pancreas, right?
A. That's correct.
Q. And they don't provide support for the notion that the drug causes diabetes by increasing insulin resistance directly?
A. Directly and acutely, yes.
Q. Right. And, in fact, as you look across

the clinical trials and look at the issue of whether or not there is -- there are statistically significant differences in looking at diabetes as an outcome, the event of diabetes, you do not see significant differences there, do you?

A. You wouldn't expect it given the duration and the size and you don't see it.

Q. And you don't see it.

MR. KANTRA: Can I have just one second, Your Honor, to consult?

THE COURT: Sure.

(Discussion off the record.)

MR. KANTRA: Dr. Brancati, thank you for your time.

THE COURT: Mr. Suggs.

MR. SUGGS: Your Honor, may I approach the bench?

THE COURT: Sure.

MR. SUGGS: I think that they opened up the door with respect to the 2007 label change. They talked about the letter from the FDA after the 2003 Consensus Statement saying that --

MR. KANTRA: That was 2004. I'm

sorry.

MR. SUGGS: -- saying that they disagreed with the consensus. It was 2004; the publication was 2004. Their letter was some months after the publication of the study. They said they disagreed with the Consensus Statement. Well, what are they doing three years later? They agreed with the Consensus Statement and required Lilly to have labeling saying that --

THE COURT: Again, you're certainly free to bring that out through other witnesses and stuff, but the purpose of this had to do with the limits of the witness' testimony and his report. His answer to that question was very clearly that he hadn't looked at anything past 2006, so if you're making a motion to ask questions based on them opening the door, I'll deny that motion.

MR. SUGGS: Okay.

(End bench conference.)

MR. SUGGS: May I have a moment, Your Honor?

THE COURT: You may.

(Discussion off the record.)

MR. SUGGS: Dr. Brancati, I just

have a few questions.

REDIRECT EXAMINATION

Q. (BY MR. SUGGS) First of all, that issue with respect to the clamp studies that were done?

A. Yes.

Q. What was the purpose of those studies in terms of their design? What were they looking at?

A. My impression is they were really looking at the -- the question of whether there's a direct and immediate ill effect of Zyprexa on the pancreas and its ability to secrete insulin or on the insulin-sensitive tissues. And to the extent that they're negative, they suggest that there is no direct effect. Than's why I said a moment ago, it made me think more of longer-term effects. Even a well-done physiologically sophisticated clamp study, it's limited by the people who are in it and by the duration of the study.

So if the effects of Zyprexa take longer than a few weeks to develop, even the best-done clamp study by the most sophisticated investigators won't detect that. But it does rule out an acute toxic effect, which was one of

the possibilities and those well-done studies rule that out.

Q. And do those studies rule out the effect of Zyprexa by indirect means by affecting weight over the long term?

A. No, and that's why I said that looking at those studies made me think more about weight gain as the mediating factor.

Q. Okay. Also, Mr. Kantra asked you some questions about weight gain over the long term, and the long course it sometimes takes for some people to develop diabetes after weight gain. Is a gain of 24 pounds in a year, is that a long-term weight gain or a short-term weight gain in your mind?

A. Well, longer than ten, weeks we've been talking about some very short-term studies. But on the grand scale, it's still fairly short term.

Q. Does Zyprexa cause diabetes, Dr. Brancati?

A. I believe it does.

Q. And did anything that Mr. Kantra asked you in cross-examination change your mind on that point?

A. No, it didn't.

MR. SUGGS: Thank you.
THE COURT: Anything further, Mr. Kantra?
MR. KANTRA: No re-cross, Your Honor.
THE COURT: Do any of the members of the jury have any questions? If you do, what I'd like you to do is what I instructed you previously, is write your question down on a piece of paper and hand them up to Mr. Borneman. I just want to make clear by asking that question, don't feel you have to give me questions. It's totally up to you.
Ms. Wallace, do you have any coming?
VENIREPERSON: I have one. I just have to look for my --
THE COURT: Who is this one from, Mark?
THE CLERK: I think it was from Ms. Mitchell, but I'm not positive -- that's right, it was from Ms. Shepherd, 12.
THE COURT: Would counsel approach, please?
Do you have any comments with that

one? Any objections to that?
MR. KANTRA: Yeah, that's a fair question.
THE COURT: I don't think I have problems with that one. I don't know whether he can answer it, but --
MR. ALLEN: I don't know -- he can ask the question --
THE COURT: I'll ask him if he knows, okay?
MR. SUGGS: I'll ask him.
THE COURT: I've got some concerns that it's appropriate for him to answer the question.
MR. ALLEN: No.
MR. FIBICH: They don't want that asked because they got him -- they tried to get him to say, you know, you didn't look at our submission, you didn't look at our submission. Your Honor, here's the fact. In January of 2007, when they got the -- the FDA got the information, they made them change the warning. Their submission was fraudulent.
THE COURT: And, again, you can ask that question from other people, but that's 2007.

I've already ruled on this, Mr. Allen.
MR. ALLEN: This is what they're doing is creating -- they say, we gave it to FDA, we gave it -- but they didn't give everything to the FDA.
THE COURT: I'm not going to give that question because I think it's outside the scope of his testimony about the validity of --
I don't have any problem with that one either.
MR. ALLEN: That's fine.
MR. KANTRA: Fine. They need to be educated on that.
THE COURT: I'll ask him the questions, then, and if we need to have follow-up we will.
Three of the four questions that I've received, I'm going to ask one of them. It will certainly be appropriate later on in the trial, but not from this witness.
Doctor, can you provide the name for -- I'm going to have trouble -- aripiprazole and ziprasidone such as olanzapine and Zyprexa? In other words, what's the trade name of those other two generic names, if you know?

THE WITNESS: You know, I'm trained at Hopkins, we use the generic names all the time. It's a matter of discipline, so that it diminishes our exposure to the brand names which are advertised. So I would need to refer to be sure.
THE COURT: Okay. Let me ask counsel: Would there be any problem if maybe tomorrow you give a stipulation to the jury as to what the trade names of these other --
MR. ALLEN: I can do it right now.
THE COURT: Well, I want to make sure that Lilly agrees with what you're going to say, Mr. Allen, and stuff. So give it to me in the form of a stipulation, and I'll read it to the jury tomorrow so that everybody knows what everybody agrees on.
This is -- if you know this: What is known about why mentally ill individuals have a greater propensity to weight gain as opposed to the general population?
THE WITNESS: That's a good question. I'll interpret it as apart from the use of antipsychotic medicines.
THE COURT: That's -- I would like

you to interpret it that way.
THE WITNESS: Yeah. It could be that they're exercising less or they're in environments where there's nothing else to do but eat more. They're confined. That's one of the thoughts, in fact, one of the hunches we're playing in a study at Hopkins aimed at improving diet and physical activity in group homes where many individuals with severe mental illness spend their daytimes.
THE COURT: And then the last question I'm going to ask you from the jurors is: Did Lilly study -- I think that means the two clamp studies -- address weight gain and its long-term effects?
THE WITNESS: Well, no. The clamp studies were designed to be short-term studies of the immediate physiologic effects of the drug, so there was really no way it could study long-term weight gain. The -- I presented the best data that I saw on weight gain, which was from that meta analysis. That was a ten-week -- only a ten-week interval, though.
THE COURT: Any followup questions from the attorneys based on those three

questions?
MR. SUGGS: Not from me, Your Honor.
MR. KANTRA: May I have a minute to confer?
THE COURT: Please.
(Discussion off the record.)
MR. KANTRA: No questions.
THE COURT: Thank you very much.
And I assume that the doctor can be excused.
MR. KANTRA: Yes.
THE COURT: Thank you very much, Dr. Brancati.
Ladies and gentlemen of the jury, that brings us to the end of our trial day. We'll resume tomorrow, same time, and if you could be in the jury room as you were today. Once again, before you leave, I'll remind you, please don't discuss this case with anyone or let anyone discuss it with you. Please try to keep an open mind and not form an opinion until you've heard all of the evidence in this case. Again, I thank you for your service, and I'll see you tomorrow.

(Jury out.)
THE COURT: Please be seated again. We're outside the presence of the jury. Anything we need to immediately take up before we leave for the day?
MR. ALLEN: Aripiprazole is Abilify and ziprasidone is Geodon.
THE COURT: Again, give me something to read in the morning and I'll read it to the jury. If you'll give me a pronunciation guide, it might be helpful as well. I just want to make -- Mr. Allen, keeping you from giving what you just said, I wasn't in any ways casting aspersions or doubting your veracity. I just feel I had to give Lilly a chance to agree with you.
MR. ALLEN: I can't believe it takes them 24 hours to agree with something like that.
THE COURT: I suspect it won't. And, again, if you all -- as I take it, there's nothing critical I have to rule on with deposition testimony or things tomorrow. So if you -- but if you can start giving me what I'm going to need to look at over the weekend. I

don't know what I'm doing tonight, but -- and it may be working on other cases. But once you get me the stuff, I can start working on it in the order that you need it.
MR. ALLEN: We'll try to get it over here -- something this afternoon, Your Honor.
THE COURT: If there's nothing else, then, we'll be in recess and I'll see everybody tomorrow.
MR. LEHNER: Thank you, Your Honor.
(Trial adjourned at 1:30 p.m.)

REPORTER'S CERTIFICATE

I, SANDRA M. MIEROP, Certified Realtime Reporter and Notary Public in and for the State of Alaska do hereby certify:

That the proceedings were taken before me at the time and place herein set forth; that the proceedings were reported stenographically by me and later transcribed under my direction by computer transcription; that the foregoing is a true record of the proceedings taken at that time; and that I am not a party to, nor do I have any interest in, the outcome of the action herein contained.

IN WITNESS WHEREOF, I have hereunto subscribed my hand and affixed my seal this 7th day of March, 2008.

_____

SANDRA M. MIEROP, CRR, CCP
Notary Public for Alaska
My commission expires: 9/18/11