

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

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

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1 PROCEEDINGS

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

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

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

1 A-P-P-E-A-R-A-N-C-E-S, continued

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

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

15 MR. BRENNER: Yes.

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

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

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

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

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

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

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

1 opening.

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

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

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

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

3 MR. ALLEN: Okay.

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

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

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

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

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

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

25 THE COURT: I'm sure I'll be

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

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

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

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

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

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

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

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

4 THE COURT: Was he deposed?

5 MR. SUGGS: Pardon?

6 THE COURT: Was he deposed?

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

9 THE COURT: So before the 2007
10 label.

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

13 THE COURT: And was there some
14 additional disclosure?

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

17 THE COURT: I'm going to let him
18 testify as to comparable rates in 2003, but the
19 2007 stuff needs to not be gone into.

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

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

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

5 MR. SUGGS: Very well, Your Honor.

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

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

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

19 MR. SUGGS: Okay. Thank you.

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

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

4 THE COURT: I'm not sure. You're
5 going to have to fashion your questions
6 carefully. Because what I hear him saying is --
7 what I understand his testimony is going to be is
8 that you're on notice of that he's going to
9 testify about comparable rates, is that not true?

10 And all he's saying is here's one more piece of
11 evidence that confirms it, and --

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

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

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

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

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

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

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

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

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

22 MR. SUGGS: Thank you, Your Honor.

23 THE COURT: Any other pretrial?

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

1 question is as we've tried to put these
2 deposition pieces together, we did file this
3 motion about the sort of word salad that's kind
4 of going to be created if we can't try to line
5 these up. We'd be happy to show you a little
6 video clip about what we're talking about or --
7 THE COURT: Well, this is -- you're
8 talking about your motion for clarification of
9 instruction regarding presentation of video
10 deposition testimony.

11 MR. LEHNER: Yes.

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

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

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

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

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

1 will consider individual applications on that
2 basis.

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

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

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

25 MR. LEHNER: Thank you.

1 MR. ALLEN: We will --

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

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

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

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

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

25 MR. LEHNER: And if we're going to

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

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

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

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

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

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

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

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

20 THE COURT: Okay.

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

24 (Break.)

25 THE COURT: Please be seated. We

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

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

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

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

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

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

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

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

13 Among the things that you should
14 consider are the following:

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

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

20 Three, what was the witness' manner
21 while testifying?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 resist the temptation to draw conclusions before
 2 you have heard all of the evidence as it may
 3 cause you to resist giving fair consideration to
 4 other evidence which is inconsistent with
 5 conclusions you have already formed.
 6 Under our system, the Plaintiff
 7 puts on its evidence and then the Defendant puts
 8 on their evidence. In order to be fair to all
 9 sides, you should work to keep an open mind until
 10 you have heard all of the evidence.
 11 Until the trial is over, you must
 12 avoid any contact with any of the persons who are
 13 participating in the trial. This includes the
 14 parties, the lawyers, the witnesses, and any
 15 persons whom you see in close contact with these
 16 individuals. Do not conduct any investigations,
 17 visit the site of events or research any issue.
 18 Remember that you are to decide the case only on
 19 the evidence presented here in court.
 20 Do not read newspaper articles
 21 about the case or watch or listen to television
 22 or radio news stories about this case until the
 23 trial is over. Do not read about this case or
 24 any matters related to this case on the Internet.
 25 If at any time during the trial you cannot see or

1 hear a witness or an attorney, please raise your
 2 hand and I will correct the situation.
 3 If you have a physical or other
 4 problem that you would like to bring to my
 5 attention, or if you feel ill or need to go to
 6 the rest room, please let me know by sending a
 7 note to the clerk or by raising your hand, and
 8 the clerk will deliver the note to me.
 9 I want you to be comfortable as you
 10 carry out your important work. Do not hesitate
 11 to inform me of any problem that you have. And
 12 ladies and gentlemen of the jury, sometimes I'm
 13 very focused on the lawyers or on the witnesses,
 14 so if I don't see you raising your hand,
 15 Mr. Borneman usually sees you and he lets me know
 16 but if we don't see you, please don't hesitate to
 17 say, Judge, I have a question. Judge, I've got
 18 something that I need to give you a note about.
 19 Something like that. If we're not noticing that
 20 you've got your hand raised, please feel free to
 21 interrupt and let us know that.
 22 I must warn you in advance that
 23 there may be delays and interruptions in the
 24 trial. Although every effort has been made to
 25 deal with matters that may cause a delay or

1 interruption before trial, there inevitably are
 2 matters that come up that must be heard outside
 3 of your presence. The purpose of having these
 4 hearings without the jury is to ensure a fair
 5 trial. I apologize in advance for these delays
 6 and interruptions, and I want to assure you they
 7 occur only to discuss important matters when
 8 necessary.
 9 Is the State ready to present its
 10 first witness?
 11 MR. SUGGS: We are, Your Honor.
 12 THE COURT: Please.
 13 MR. SUGGS: Your Honor, ladies and
 14 gentlemen of the jury, the State of Alaska calls
 15 Dr. Fred Brancati as an expert witness.
 16 THE COURT: And sir, if you could
 17 remain standing behind the witness' chair, we'll
 18 put you under oath.
 19 FREDERICK BRANCATI,
 20 Having been duly sworn by the
 21 clerk, testified as follows:
 22 THE CLERK: For the record, sir,
 23 please state your full name, spelling your first
 24 and last name.
 25 THE WITNESS: My name is Frederick

1 Brancati. Last name is B as in boy,
 2 r-a-n-c-a-t-i. First name Frederick,
 3 F-r-e-d-e-r-i-c-k.
 4 THE COURT: Mr. Suggs.
 5 DIRECT EXAMINATION
 6 Q. (BY MR. SUGGS) Good morning,
 7 Dr. Brancati.
 8 A. Good morning.
 9 Q. Where do you live, sir?
 10 A. I live in Lutherville. It's just
 11 outside Baltimore, Maryland.
 12 Q. I want to thank you for traveling about
 13 5,000 miles from Baltimore to come here to
 14 testify on behalf of the State of Alaska.
 15 Have you ever testified in trial
 16 before?
 17 A. Just briefly in a -- in a custody case
 18 for the hospital, but never in anything like this
 19 before.
 20 Q. Okay. And what is your occupation, sir?
 21 A. I'm a physician and a faculty member at
 22 Johns Hopkins University.
 23 Q. And has the State retained you as an
 24 expert witness to testify about diabetes and
 25 whether or not the use of Zyprexa increases the

1 risk of diabetes?
 2 A. They have.
 3 Q. And has the State also retained you to
 4 testify about whether Zyprexa causes more
 5 diabetes than other antipsychotic drugs?
 6 A. They have.
 7 Q. Okay. And have you prepared a report
 8 regarding your opinions on those issues and the
 9 basis for your opinions?
 10 A. Yes.
 11 Q. And I don't believe you have that report
 12 with you, do you, sir?
 13 A. No, I don't.
 14 MR. SUGGS: Your Honor,
 15 Dr. Brancati's report is Plaintiff's Exhibit
 16 10127. I'm not going to be offering it into
 17 evidence, but counsel have a prior agreement that
 18 their respective expert witnesses may have their
 19 reports with them when they testify for
 20 reference, if necessary.
 21 THE COURT: And that is true?
 22 MR. LEHNER: Yes.
 23 THE COURT: And that's the rule
 24 we'll follow.
 25 MR. SUGGS: Very well, Your Honor.

1 Q. (BY MR. SUGGS) Dr. Brancati, before we
 2 talk about your opinions about Zyprexa, I'd first
 3 like to ask you some questions about your
 4 background, your training and experience in the
 5 field of diabetes.
 6 First off, sir, how old are you?
 7 A. I'm 48.
 8 Q. You're married?
 9 A. I'm married.
 10 Q. Your wife is a doctor also. Is that
 11 correct?
 12 A. Yes, also at Hopkins.
 13 Q. Thank you. And you have two children?
 14 Two 11-year-old girls? Correct?
 15 A. Twins.
 16 Q. And you grew up in Queens, in New York
 17 City?
 18 A. Yes, and then Long Island.
 19 Q. I believe you went to undergraduate
 20 school at University of Harvard, correct? Or
 21 Harvard University?
 22 A. Harvard University.
 23 Q. And you graduated in 1981; is that
 24 correct?
 25 A. That's correct.

1 Q. And you graduated magna cum laude,
 2 correct?
 3 A. Correct.
 4 Q. And then you went to medical school
 5 after that?
 6 A. Medical school at Columbia University in
 7 New York City.
 8 Q. And what year did you graduate from
 9 medical school?
 10 A. Graduated in 1985.
 11 Q. And did you then take an internship and
 12 residency?
 13 A. Yes, I did, at the University of
 14 Pittsburgh.
 15 Q. In what field?
 16 A. That was in internal medicine.
 17 Q. And what is meant by the phrase
 18 "internal medicine"?
 19 A. Internal medicine is the training ground
 20 for physicians who practice diagnosis and
 21 treatment of conditions in -- in adults. Many
 22 trainees go on to careers in organ-oriented
 23 specialties like cardiology and pulmonary
 24 medicine. I stayed in general internal medicine.
 25 Q. And you were in that residency program

1 from 1985 through 1989; is that correct?
 2 A. Yes, three years of residency and then a
 3 year as a chief resident.
 4 Q. What were your responsibilities as chief
 5 resident?
 6 A. The chief resident is one of the leaders
 7 of the residency program, making schedules,
 8 teaching, organizing the practice of the
 9 trainees.
 10 Q. And after you completed your residency,
 11 did you then go on to get a post-doctoral
 12 fellowship in internal medicine at Johns Hopkins
 13 University School of Medicine?
 14 A. Yeah. I was interested in research, and
 15 so I went to Johns Hopkins for a three-year
 16 post-doctoral fellowship. It was in the division
 17 of internal medicine and the main attraction was
 18 the ability to train in epidemiology.
 19 Q. And that was from 1989 through 1992 that
 20 you were in post-doctoral fellowship?
 21 A. That's correct.
 22 Q. Do most physicians in internal medicine
 23 have such post-doctoral fellowships that they
 24 engage in?
 25 A. Many graduates of medicine residency

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

6 Q. You went into the research side of it?

7 A. Yes.

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

10 A. That is correct.

11 Q. What is epidemiology?

12 A. Epidemiology is the study of patterns of
13 disease in populations with an aim to identify
14 causes of disease as a means to develop
15 strategies for prevention. It started in the
16 field of infectious diseases and that's where the
17 term epidemics come from. But in the past 30 or
18 40 years scientists have taken the methods
19 they've learned from the study of infectious
20 disease and figured out how to apply it to
21 chronic diseases like heart disease, obesity or
22 diabetes.

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

1 A. Yes, 1992.

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

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

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

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

13 Q. Sorry.

14 A. That's okay.

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

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

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

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

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

13 Q. What is the focus of your research?

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

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

1 A. Yes.

2 Q. Okay. And where does that fee go?

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

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

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

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

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

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

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

6 Q. And why are the reviews anonymous?

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

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

21 A. Yeah.

22 Q. About how many?

23 A. About 150.

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

1 A. The majority; 120 or so.

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

4 A. Yeah, for many journals.

5 Q. For how many?

6 A. Fifteen or so.

7 Q. And what are national advisory
8 committees?

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

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

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

1 you've been a member of national advisory
2 committees?

3 A. Yeah, many.

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

6 A. Yes.

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

9 A. Yes, I have.

10 Q. Which ones?

11 A. Most recently Pfizer and Novartis.

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

15 A. Sure.

16 Q. First off, am I correct there are
17 basically two types of diabetes, type 1 and type
18 2?

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

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

24 A. Sure. Type 1 is the less common type.

25 About 5 percent of diabetes cases in the U.S. end

1 up being called type 1. That's the type that

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

10 Type 2 diabetes also involves
11 elevations in blood sugar and blood glucose, but
12 occurs in much different group of people. Type
13 2, which accounts for 90 percent or so of the
14 prevalent cases in the U.S., tends to occur in
15 middle-aged individuals who are overweight,
16 sedentary. The problem there -- they get high
17 blood sugar, but it's not because the pancreas is
18 inflamed and unable to secrete insulin. The
19 problem with them is that they become
20 insulin-resistant. The body is requiring greater
21 and greater amounts of insulin just to keep pace,
22 and the pancreas fails to compensate. The
23 balance is lost and they get diabetes even though
24 the pancreas is making large quantities of
25 insulin.

1 Q. Is there scientific evidence
2 demonstrating that Zyprexa is associated with an
3 increased risk of type 2 diabetes?

4 A. I believe there is, yes.

5 Q. Am I correct that there is not any type
6 of evidence linking Zyprexa with type 1?

7 A. There is some data linking Zyprexa to
8 ketoacidosis, which is one of the hallmarks of
9 type 1, but the bulk of evidence that I found was
10 in relation to type 2 diabetes.

11 Q. Before we talk about the linkage between
12 Zyprexa and type 2 diabetes, let's talk in detail
13 about just what type 2 diabetes is and how it
14 develops.

15 And have you prepared some slides
16 to show the jury that will help us explain what
17 type 2 diabetes is?

18 A. I have.

19 Q. Okay. The first one is entitled --

20 MR. SUGGS: Hard to hear me or
21 the --

22 THE COURT: Ladies and gentlemen,
23 are you having trouble hearing the witness?

24 Thank you very much for moving the
25 microphone. See if that cures it.

1 Q. (BY MR. SUGGS) The first slide that you
2 prepared is called Type II Diabetes Mellitus.
3 Did I pronounce that right -- it's mellitus or
4 mellitus?

5 A. It can go either way. I say mellitus.
6 It's from words meaning sweet urine. Diabetes is
7 from a word meaning outflow, and mellitus is from
8 Latin meaning sweet. That's how in the days
9 before laboratories, the condition was diagnosed
10 as sweet-tasting urine or urine that would
11 attract flies.

12 THE COURT: Mr. Suggs, before we go
13 further, I assume you're offering the doctor as
14 an expert in the field of diabetes?

15 MR. SUGGS: Yes, Your Honor.

16 THE COURT: Any objection or any --

17 MR. KANTRA: As what?

18 MR. SUGGS: As an expert in the
19 field of diabetes.

20 MR. KANTRA: I just have a couple
21 questions, if I might.

22 VOIR DIRE EXAMINATION

23 Q. (BY MR. KANTRA) Dr. Brancati, you're
24 not here today to offer an opinion with respect
25 to a reasonable degree of medical certainty with

1 respect to whether or not Zyprexa causes type 1
2 diabetes, right?

3 A. No.

4 Q. And you are not a physiologist, are you?

5 A. That's correct, I am not.

6 Q. Which means that you're not somebody who
7 specializes in conducting studies to evaluate the
8 mechanisms by which diabetes occurs?

9 A. That's right.

10 Q. So, for example, you've not done studies
11 which would look at -- clamp studies to look at
12 whether a drug might affect a pancreas, for
13 example?

14 A. That's correct.

15 Q. And I also am correct in saying that
16 you're not a psychiatrist?

17 A. That's right.

18 Q. You don't run a psychiatric clinic?

19 A. No, I do not.

20 Q. And you don't make the risk-benefit
21 analyses that psychiatrists and other physicians
22 might make in deciding whether to prescribe
23 antipsychotic medications?

24 THE COURT: Mr. Suggs.

25 MR. SUGGS: Your Honor, I think

1 this goes beyond the scope of what's
2 necessary to --

3 THE COURT: So do I.

4 MR. KANTRA: Just establishing the
5 boundaries, sir. With that, my only objection
6 would be that he be offered as an expert witness
7 with respect to type 2 diabetes and not type 1,
8 since he's not offering that.

9 THE COURT: Any objections to that
10 clarification?

11 MR. SUGGS: No, Your Honor.

12 THE COURT: Then I'll recognize him
13 as that, as an expert and will be discussing type
14 2 diabetes.

15 MR. SUGGS: Your Honor, the State
16 takes the position that Dr. Brancati is clearly
17 an expert with respect to both types of diabetes.
18 We're offering his testimony about type 2 and
19 that's essentially -- you've heard all the
20 testimony we're going to have about type 1.

21 THE COURT: Okay. I will recognize
22 him for that purpose.

23 MR. SUGGS: Thank you, Your Honor.

24 THE COURT: Go, on Mr. Suggs.

25 Q. (BY MR. SUGGS) Okay. We were talking

1 about diabetes mellitus, and I believe you said
2 it was originally called sweet water?

3 A. Sweet urine. That's where the name
4 comes from.

5 Q. Sweet urine. You say it was diagnosed
6 in the olden days by tasting urine?

7 A. Uh-huh, believe it or not.

8 Q. Thank you. Glad I didn't have that job.

9 You note there that type 2 is by
10 far the most common in the U.S. How common is
11 it, sir?

12 A. There -- current estimates is that there
13 are about 20 million individuals in the United
14 States with diabetes and about 90 percent of
15 those, 9-0, are thought to have type 2 diabetes.

16 Q. Can you track us through the bullet
17 points and explain what you've prepared for us?

18 A. As I've said a moment ago, type 2
19 typically occurs in middle-aged, overweight,
20 inactive people. The conventional wisdom is that
21 this is the typical sequence of events. That you
22 have someone who starts off as a young adult who
23 is lean and active, and they gradually gain
24 weight as they go towards middle age. And weight
25 gain -- because of increased calorie intake and

1 decreased calorie expenditure in the form of
2 exercise and so weight deposits and then that
3 weight gain is associated with insulin
4 resistance.

5 Q. Sorry. I was going to ask you what
6 insulin resistance is.

7 A. Sure, sure. Well, for the body to
8 maintain a stable label of glucose, the pancreas
9 serves as a bit of thermostat. It senses the
10 level of glucose or sugar in the blood. As that
11 level rises, the pancreas secretes insulin. And
12 then the response of the body depends on a prompt
13 response to the insulin-sensitive tissues to that
14 signal.

15 What happens is as people gain
16 weight and reach middle age is they'll develop
17 resistance to that insulin signal or it will take
18 more and more insulin to generate the same
19 response of the body to incorporate glucose from
20 the blood into the insulin-sensitive tissues like
21 fat and liver and muscle. As long as the
22 pancreas compensates by making more insulin, by
23 sending out more hormone, the balance is
24 maintained and the glucose levels stay steady.
25 But unfortunately, in many people the pancreas

1 fails to compensate. It's still secreting a lot
2 of insulin, just not enough required for that
3 individual to keep glucose levels steady. Then
4 the blood sugar rises and a bit of a vicious
5 cycle steps in, because as blood sugar rises, the
6 function of those insulin-secreting cells becomes
7 less efficient, so they secrete a little less
8 insulin. A little less insulin, a little higher
9 sugar; a little higher sugar, a little less
10 insulin; vicious cycle and then diabetes
11 develops.

12 Q. Are there early symptoms of type 2
13 diabetes?

14 A. There are.

15 Q. And did you prepare a slide that shows
16 what those symptoms are as well?

17 A. I did.

18 Q. What are the early symptoms of type 2
19 diabetes?

20 A. So this -- this slide lists a variety of
21 symptoms. Many people will have some and some
22 will have all, depending on their particular
23 circumstances. So one of the cardinal signs is
24 increased urine production. People will notice
25 that they're urinating more frequently, that the

1 volume of the urine is larger each time they go,
2 that if they've not been urinating at night, they
3 might notice they're getting up at night. If
4 they have been, they might notice that they're
5 getting up more or the volumes at night are
6 greater.

7 As fluid goes through the body,
8 they become thirsty. The fluid intake -- the
9 body prompts the person with diabetes to consume
10 more fluid to stay even and stave off
11 dehydration.

12 The other thing that happens
13 because calories are flowing out in the urine.
14 Now the sugar that goes out in urine, that's real
15 calories. It starts to pull calories from the
16 body, and that will lead to increased hunger as
17 if the individual had been exercising and burning
18 calories that way. So people will report
19 increased hunger and they're eating more, but
20 ironically they're more hungry, they're eating
21 more, but they'll have weight loss. Some of that
22 weight loss is from the calories going out in the
23 urine. Some of the weight loss is fluid that's
24 going out being pulled along with the glucose.

25 As sugar levels rise higher, and as

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

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

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

17 A. Yes.

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

21 A. I have.

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

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

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

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

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

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

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

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

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

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

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

11 A. We do.

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

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

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

1 not talking about us today, right?

2 THE WITNESS: That's correct. In
3 scientific medical jargon, a trial is an
4 experiment in humans, and typically the design is
5 you take a group of people at risk for some
6 complication. In the case of Look Ahead, we have
7 people with diabetes at risk for heart disease.
8 We flip a coin and assign half the study
9 participants to one condition. In this case,
10 it's just their usual care. And we flip a coin
11 and assign the other group of individuals to
12 another question and Look Ahead, it's intensive
13 coaching about weight loss.

14 And then the trial component, you
15 follow both groups forward over time and you look
16 for systematic differences in the occurrence of
17 those complications.

18 THE COURT: Thank you.

19 MR. SUGGS: Thank you, Your Honor.

20 Q. (BY MR. SUGGS) This chart shows at the
21 top, food in the form of carbohydrates going into
22 the stomach and then apparently getting converted
23 to sugar.

24 Is it only carbohydrates that are
25 used by the body to make sugar?

1 A. We show carbohydrates here because
2 that's the constituent of the diet that's most
3 directly converted to glucose, but the liver,
4 part of the liver's job in the body is to be a
5 clearinghouse for all different types of food
6 substances. And part of what the liver does is
7 it can take protein, convert it to carbohydrate;
8 take carbohydrate, convert it to protein; convert
9 both of those to fats. That's the liver's job
10 but we just show carbohydrate here as an example.

11 Q. Can you walk us through the chart
12 starting at the top, and how the body processes
13 food.

14 A. Sure. So this is north in the body.
15 This is south, so people eat food, it goes into
16 the stomach. It's acted on by digestive enzymes
17 and for carbohydrates that releases a lot of
18 sugars into the blood system. So this tube here
19 represents the blood system around the gut. The
20 S's represent molecules of sugar or glucose. The
21 I represents molecules of insulin.

22 When sugar is released into the
23 bloodstream, that signals the pancreas to act.
24 This is the pancreas, it's about the size of your
25 fist, and it sits back behind the pit of the

1 stomach. We usually don't think about it much.
2 Much of the substance of the pancreas is devoted
3 to making pancreatic juices, enzymes that help
4 digest foods, especially fat. But if you slice
5 it and look under a microscope, you see small
6 islands of cells.

7 They're actually called islet
8 cells. And they're the insulin-secreting cells
9 of the pancreas. They're very well-positioned to
10 sense the levels of sugar in the blood and so
11 they're poised to respond quickly. When the
12 sugar level goes up, the insulin secreted by the
13 pancreas -- the insulin goes all over the body
14 through the blood supply. And it specifically
15 triggers three types of tissue to take sugar or
16 glucose out of the blood and into that organ.
17 And those insulin-sensitive organs are liver,
18 muscle and fat, fat all over the body.

19 Q. How is it that insulin regulates the
20 activity of sugar or the presence of sugar?

21 A. For these three types of organs, sugar
22 can't get into -- can't get from the bloodstream
23 into the organ without insulin more or less
24 unlocking the door.

25 Q. Do you have a slide showing that?

1 A. Oh, yes. Yes, I do. So, in fact,
2 here's the lock and the key. These are fat
3 cells, a rim of cell, and then a big fat droplet
4 on the inside. This is sort of the way they look
5 under the microscope. And even if there's sugar
6 bathing that tissue, it won't go in unless
7 there's insulin there to send a signal to the
8 cell to actively take the sugar from the
9 bloodstream into the fat cell. If there's no
10 insulin circulating, as in kids with type 1
11 diabetes, who get inflamed pancreases, that's a
12 problem where sugar will build up in the
13 bloodstream and cause diabetes.

14 In people with type 2 diabetes,
15 there's plenty of insulin floating around. The
16 trouble is some of the keyholes are blocked and
17 it doesn't signal properly and the sugar backs up
18 into the blood supply for that reason.

19 Q. And what is it that makes those cells
20 resistant to insulin?

21 A. That's a great question. There's still
22 a lot of active research on that but we know a
23 lot more than we did ten years ago. When I was
24 coming through training, the thought was that,
25 for example, fat tissue was really inert. It was

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

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

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

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

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

1 likely to have insulin resistance than leaner
2 individuals.

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

8 A. Exactly. So that's what's thought to
9 happen when you see blood sugars rise from the
10 normal range, which might be in the 80 to 90
11 range. And they -- they rise -- they can rise to
12 100, 105, 110 as -- still not in diabetic range,
13 but now in that 100 to 125 range which we call
14 impaired fasting glucose. Those are individuals
15 who seem to be on their way to getting diabetes,
16 and it's a high-risk group that's been targeted
17 by public health agencies and the federal
18 government in diabetes prevention strategies.

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

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

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

8 A. Yeah, hyperglycemia can refer to
9 increases in blood sugar across a whole range.
10 So, for example, in the general population a
11 normal level in a middle-age adult might be 85 or
12 90. For that individual, if they go from 85 to
13 90 to 105, they're showing some degree of
14 hyperglycemia because it's high compared to where
15 they were or it's high compared to a normal
16 population.

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

25 Q. I've heard doctors sometimes talk about

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

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

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

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

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

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

1 anything other than diabetes?

2 A. No, unless they happen to be in the
3 hospital and have glucose running intravenously
4 and have some external source of blood sugar then
5 in clinical practice it's really diabetes
6 mellitus.

7 Q. Thank you. So would it be fair to say
8 that if you did a randomized study where you gave
9 one group of patients a particular treatment and
10 after that they then showed -- that group showed
11 hyperglycemia, what would you -- what would you
12 take from that?

13 A. If it's hyperglycemia in the frankly
14 diabetic range, 126 or greater, then I'd conclude
15 that the drug is provoking episodes of -- of
16 diabetes. If it's -- if it's hyperglycemia,
17 still in the nondiabetic range, it would make me
18 worry that the drug is pushing individuals from a
19 normal state to insulin resistant to impaired
20 fasting glucose on the way to diabetes, but maybe
21 not yet.

22 Q. We talked about how hyperglycemia occurs
23 in diabetes. Why do we care if somebody is
24 hyperglycemic? What's the result of having too
25 much sugar in the blood?

1 blood vessel disease we can see in vessels --
2 vessels we can see with the naked eye. We can
3 see the disease with the naked eye. So when we
4 go to medical school and we dissect, we learn.
5 We can see the vessels of the heart, the coronary
6 arteries; we can see the vessels that lead to the
7 brain, the carotid arteries; and the vessels that
8 lead to the leg, the femoral arteries. And
9 macrovascular disease is the term that diabetes
10 researchers use for what other physicians and
11 researches call atherosclerosis or blockage of the
12 arteries from cholesterol deposits, inflammation
13 and superimposed clot.

14 Q. And is there a higher incidence of
15 macrovascular disease in diabetes?

16 A. Yes, there sure is. Macrovascular
17 disease can occur and does occur in people
18 without diabetes. The trouble with -- the
19 problem for people with diabetes is that they
20 have a much accelerated process compared to
21 nondiabetic individuals. They are at much higher
22 risk.

23 Q. And do we know why that is?

24 A. A lot of different theories, but like
25 everything else related to diabetes, it's

1 A. Well, I mentioned some of the short-term
2 problems which could be troublesome, but the real
3 problems is with diabetes in general type 2
4 diabetes, in particular, are the long-term
5 vascular complications, the damage to the large
6 and the small vessels in the body.

7 Q. Do you have a chart or slide rather,
8 that summarizes that?

9 A. I do.

10 Q. Actually, before we get to that -- I
11 take it back, let's go right there.

12 This slide that you prepared is
13 entitled, Diabetes Leads to Long-term Health
14 Problems and Death by Damaging Blood Vessels.
15 And you've got two headings in there. The first
16 is macrovascular disease.

17 Can you explain what you mean by
18 that phrase macrovascular disease?

19 A. Well, let me make the contrast between
20 macro and micro. Macro is a prefix that means
21 big or visible to the naked eye in this case;
22 micro means small or too small to be seen by the
23 naked eye. You need a microscope. And vascular
24 means blood vessels, or the tubes that carry
25 blood. So macrovascular disease is the type of

1 multifactorial. Some of the theories have to do
2 with modification of the cholesterol which is
3 involved in creating the blockage so that it's
4 more likely to deposit. Another line of
5 reasoning has to do with inflammation inside the
6 body, really around the body in such a way that
7 the -- that the smooth lining of the blood vessel
8 is damaged or creates an area for deposition of
9 cholesterol.

10 Another theory has to do with the
11 effects of high blood sugar on platelets, the
12 small elements in blood that are involved in
13 forming clots. So there's a variety of different
14 pathways to atherosclerosis.

15 Q. You've used the term atherosclerosis now
16 a couple of times. Do we have a chart or
17 actually a picture that shows that process?

18 A. We do.

19 Q. Can you tell us what this depicts?

20 A. Sure. So this is a cross-section of,
21 say, a coronary artery. So this would be if you
22 have the artery like this and snip it and look at
23 it down longways into the opening. This is what
24 you'd see in a normal vessel. Three layers of
25 tissue here, the endothelium here and the blood

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

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

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

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

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

17 Q. Why does a clot form?

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

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

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

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

17 A. I did.

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

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

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

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

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

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

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

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

17 A. All the same.

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

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

1 scar.

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

4 Do you have a slide showing that as
5 well?

6 A. I do.

7 Q. What does this slide depict?

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

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

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

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

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

9 A. That's correct, especially the legs.

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

12 A. We do.

13 Q. Tell us what is shown on these pictures.

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

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

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

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

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

25 A. I do.

1 Q. And what is this picture showing?

2 A. This is the foot of someone with
3 diabetes. You see here the tips of the toes and
4 in this case the entire toe has essentially just
5 died, turned black, and gradually worn -- worn
6 away because of lack of blood supply.

7 Q. Okay. So we've now talked about
8 atherosclerosis in the big vessels that can
9 impact the heart, the brain and the limbs.

10 Have we covered the macrovascular
11 side of the problem?

12 A. Yes.

13 Q. Okay. Let's go back and take a look at
14 the microvascular side of this.

15 This is the slide we looked at
16 earlier. But could you focus on the
17 microvascular portion of the slide and describe
18 for us what is involved in microvascular disease?

19 A. Sure. Macro is you can see with the
20 naked eye. Microvascular disease is disease of
21 the small vessels; the ones you can only see with
22 the microscope. There are three vessel beds we
23 are particularly concerned about in diabetes; the
24 retina, which is the screen in the back of the
25 eye that lets us see; the kidney and the nerves,

1 especially the nerves of the leg. One thing
2 that's different about micro versus macrovascular
3 disease, not only which vessels are infected, but
4 how typical it is of diabetes. Nondiabetic
5 individuals get macrovascular disease all the
6 time. It's just very accelerated in diabetes.

7 Microvascular disease really occurs
8 only in people with diabetes. You don't see this
9 kind of damage in people who don't have diabetes.
10 The main reason is that because the bad actor is
11 the high blood sugar causing damage to these
12 vessel beds. When high blood sugar damages the
13 small vessels of the retina, we call that
14 retinopathy. Pathy just means disease, so it's
15 retinopathy -- disease of the retina -- it's
16 diabetic and it's the leading cause of acquired
17 blindness in the United States.

18 Nephropathy or disease of the
19 kidney due to diabetes. That's the leading cause
20 of kidney failure in the United States, which
21 used to be uniformly fatal before dialysis. Now
22 diabetic nephropathy is the leading cause for
23 Americans to go on hemodialysis.

24 And neuropathy is disease of the
25 vessels leading to the nerves, especially in the

1 leg. It turns out to be the leg that's affected
2 because those nerves are the longest. They go
3 from the spinal cord all the way down to the leg.
4 So they're more vulnerable to lack of blood
5 supply, oxygen and nutrients. Neuropathy can
6 first lead to pain in the absence of any sort of
7 pressure. For example, the type of pain that
8 people get with shingles, it's a nerve pain.
9 Very troublesome. Then there also could be
10 sensation loss, which is ironic given they could
11 have pain but also lose a sensation. So the big
12 worry in people with severe diabetic neuropathy
13 is they'll step on a nail and not notice it until
14 the foot's infected. So the sensation loss can
15 be that profound.

16 And then the sensation loss, the
17 risk of trauma and injury to the leg and the
18 likelihood they may not find infections early
19 when they happen all predispose to serious
20 infection, gangrene and limb loss.

21 Q. Let's focus on the retinopathy or the
22 blindness part of it first. Let me pull up
23 another slide and can you describe for us what's
24 involved -- some more detail with respect to
25 diabetic retinopathy.

1 A. Sure. As I mentioned, hyperglycemia or
2 high blood sugar is the culprit here, the small
3 vessels, the microscopic vessels of the retina.
4 If it causes some damage directly, it damages the
5 wall of those vessels so they get, on the one
6 hand leaky, on the other hand blocked. So the
7 retina -- the retina experiences a loss of
8 oxygen. It attempts to compensate by growing out
9 new vessels to bring in blood supply around those
10 blockages. The trouble is that the new vessels
11 are really quite fragile and they don't grow just
12 in places where they should grow, so it creates
13 problems for the eye. It's an adaptation that
14 turns out to be dangerous. A maladaptation.

15 And so diabetic eye disease,
16 diabetic retinopathy can interrupt vision in a
17 variety of different ways. The leakage of the
18 fluid and the proteins from the vessels, if that
19 leakage occurs over the part of the retina
20 problem that's involved in visual acuity called
21 the fovea, that can lead to blindness. The new
22 vessels grow out; they're very fragile. If they
23 rupture and bleed and the bleeding occurs over
24 the point of visual acuity, over the fovea, you
25 can get blindness from that.

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

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

18 A. We do.

19 Q. Tell us what this slide shows.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 A. We do.

14 Q. If I can get this to work.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23 A. That's right.

24 Q. Okay. Let me go to that.

25 If I can. There we go.

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

3 A SPEAKER: You did it.

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

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

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

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

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

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

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

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

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

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

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

5 We'll be in recess for about 15
6 minutes.

7 (Break.)

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

10 Mr. Suggs.

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

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

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

4 Q. Does association necessarily means
5 causation?

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

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

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

23 A. Yeah.

24 Q. What do you mean by that?

25 A. Commonly know -- the term risk factor is

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

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

1 should go after that risk factor as a means to
2 prevent its health consequences.

3 Q. When epidemiologists use the term risk
4 factor, does that imply that there is some sort
5 of causal relationship?

6 A. Yeah. I'll say that some of my
7 colleagues disagree about the precise terminology
8 because there's no authority that governs the
9 language specifically, but I'll tell you what I
10 do and what we commonly do at Johns Hopkins is
11 that -- I use the term risk factor when I'm
12 thinking that the relationship is probably
13 causal. I say probably because it's often
14 impossible to prove with 100 percent certainty a
15 causal relationship.

16 Take the circumstance with
17 cigarette smoking and lung cancer. We have
18 incredibly strong evidence that cigarette smoking
19 leads to lung cancer, but no one has ever done
20 the definitive experiment to prove it with 100
21 percent certainty. That experiment would be to
22 take thousands of people at risk for lung cancer
23 who don't smoke, flip a coin, randomly assign
24 some of those folks in that group to smoking,
25 others in that group to nonsmoking and then

1 continue that for 10, 20, 30 years and count up
2 the number of lung cancers in each group. Can't
3 do that. It's not ethical because there's no
4 presumed health benefit to smoking; it's a
5 harmful exposure. So you could never do that
6 kind of randomized control trial. You'd never
7 get 100 percent certainty.

8 Take another example.
9 Epidemiologists like to study common components
10 of the diet, for example, coffee drinking. I
11 like drinking coffee, so I follow that literature
12 closely. It wouldn't be unethical to do that
13 sort of study if one were interested in the
14 potential relationship between coffee consumption
15 and heart attack, for example. You could
16 conceivably take thousands of people and
17 ethically randomize half to coffee consumption
18 and the other half not. It would just be very
19 difficult to do. It's not an ethical problem,
20 it's a logistical problem. How do you get people
21 who feel completely balanced about coffee
22 consumption or not and take half of them and have
23 them drink it for 10 or 20 years?

24 So there are some answers that we
25 never get to 100 percent certainty, and that's so

1 often true that in epidemiology, we often -- a
2 lot of our investigative battle is to get
3 relationships from the point of just a vague
4 association to the point that we say, yeah, this
5 is looking like a risk factor, we have enough
6 information to act on, either at the clinical
7 level in the office or at the public health level
8 in terms of policy.

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14 association to the point that we say, yeah, this
15 is looking like a risk factor, we have enough
16 information to act on, either at the clinical
17 level in the office or at the public health level
18 in terms of policy.

19 Q. And when epidemiologists say that some
20 factor, whether it's a drug or chemical agent or
21 whatever increases the risk of developing a
22 disease, does that imply also that there is a
23 causal relationship?

24 A. Yeah, it implies that we're definitely
25 thinking there's a causal relationship. Now, for

1 example, I wouldn't say that gray hair increases
2 the risk of heart attack. I'd say gray hair is a
3 predictor. But when I use the same increases the
4 risk of it, yeah, I'm thinking it's potentially
5 causal. It could always be proved otherwise in a
6 definitive, large-scale study but we rarely get
7 to that point. Often in epidemiology where we're
8 on the track for identifying new risk factors and
9 seeing how strong it is, we're doing studies and
10 looking at evidence to see if we can move that
11 factor from a mere association into the range
12 where we say this is looking like a risk factor.

13 Q. And how do epidemiologists know if a
14 risk factor is for real as opposed to just some
15 sort of quirky statistical fluke?

16 A. There are a variety of criteria that we
17 apply were developed in the 1960s, specifically
18 in relation to the study of cigarette smoking.
19 Because there was a lot of disagreement in the
20 '50s and '60s about just how harmful cigarette
21 smoking was. There was no prospect of doing a
22 definitive, randomized, controlled human
23 experiment to determine -- to determine the risk
24 unequivocally. And epidemiologists were doing a
25 lot of work that was observational. Not randomly

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

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13 that problem and develop a set of criteria that
14 could be used to sort out associations without
15 any likely causal link from risk factor
16 associations where it looked increasingly likely
17 that there was a causal connection.

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

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

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

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

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

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

24 A. Sure. I'd be delighted.

25 So one criterion is the strength of

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

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

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

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

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

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

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

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

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

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

1 80 pack years of smoking, someone who has smoked
2 two packs a day for 40 years, they're at much
3 higher risk than someone who's just had 10 pack
4 years of smoking and quit. So we know that with
5 cigarette smoking there's a strong biological
6 gradient or a strong dose response. That also
7 adds to the evidence for causality.

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

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

25 So, with smoking and lung cancer,

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

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

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

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

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

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

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

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

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

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

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

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

1 conceptualize; it's very hard to do.
 2 Sometimes, though, we do have
 3 experimental evidence like that. Often the
 4 experimental evidence is a little more modest, a
 5 little more short-term. For example, there was
 6 never the prospect of doing that kind of large,
 7 long-term study in cigarette smoking because of
 8 the ethical concerns, but there were a number of
 9 short-term studies taking healthy nonsmokers,
 10 having them smoke for short periods of time in
 11 controlled circumstances, in hospital research
 12 units, and then looking at short-term effects on
 13 their lung function, for example.
 14 Those -- those sorts of experiments
 15 could be done and they added to the body of -- of
 16 evidence. In other circumstances, it's possible
 17 to do -- when it's impossible to do a study that
 18 lasts 10 or 20 years, it might be quite feasible
 19 to do a study that lasts six or 12 months. In
 20 those cases one might not be able to count on
 21 having the complication itself, the event itself,
 22 for example, lung cancer or serious emphysema
 23 leading to death, but one could find upstream
 24 abnormalities that are on the pathway to the
 25 complication.

1 For example, they might not have
 2 full-blown emphysema that restricts them to bed
 3 and oxygen, but they might have chronic
 4 bronchitis which is on the way to developing
 5 full-blown emphysema. You could test that in the
 6 short-term experiment and that would add to the
 7 experimental -- that would add to the evidence
 8 base in favor of causality.
 9 Q. Dr. Brancati, regarding diabetes, in
 10 particular, and leaving aside for a moment the
 11 question of whether Zyprexa is involved in
 12 diabetes, are there risk factors for diabetes
 13 that are well established and accepted in the
 14 field of medicine?
 15 A. Yes, there are.
 16 Q. And let me pull up this next slide, Risk
 17 Factors for Type 2 Diabetes. Can you very
 18 briefly describe for us the risk factors that are
 19 on this slide?
 20 A. Sure. I've grouped them into two
 21 categories modifiable and nonmodifiable. It's
 22 just the jargon we use to mean the factors we can
 23 do something about; the factors we can change or
 24 modify, and the factors we can't do anything
 25 about. The ones we can't do anything about, we

1 don't fret too much over them, except that we
 2 know that they can be used for risk prediction,
 3 identifying which group's at highest risk to go
 4 after the modifiable factors.
 5 So the nonmodifiable factors for
 6 type 2 diabetes that are well established, one is
 7 age. As people get older, they're more and more
 8 likely to have type 2 diabetes. Type 2 diabetes
 9 is unusual in kids and young adults. Can happen.
 10 It's happening more in this country, but it's a
 11 strong risk factor.
 12 Another factor is race and
 13 ethnicity. It turns out in the United
 14 States that people of European ancestry, we get a
 15 lot of diabetes, but we get a lot less than
 16 people of every other ethnic group in the United
 17 States. So, African-Americans are at higher
 18 risk, Hispanic Americans are at higher risk,
 19 Native Americans, Pacific Islanders, Native
 20 Alaskans, all of those other ethnic groups are at
 21 higher risk than their European counterparts.
 22 The third there is family history.
 23 I think that's something we all know, that
 24 diabetes runs in families, especially type 2
 25 diabetes. It's always one of the questions we

1 ask -- that I ask when someone comes in and
 2 they're concerned about getting diabetes. I know
 3 their age, their race, ethnicity. I also ask
 4 them about a history of diabetes in the family.
 5 If there's been a lot of it, I worry that they're
 6 at high risk.
 7 Q. And then over on the right-hand side you
 8 have the modifiable risk factors. Am I correct
 9 that those are the ones that can be altered by
 10 behavioral changes to some extent?
 11 A. That's correct. These are the ones we
 12 have a shot at doing something about. So obesity
 13 is the single strongest risk factor for type 2
 14 diabetes. The gradient of risk across the full
 15 range of obesity, from lean all the way up to
 16 morbidly obese, is well over tenfold. So it's
 17 like over the full range of the relationship
 18 between cigarette smoking and lung cancer. It is
 19 the single biggest risk factor. That's why it's
 20 been the target in studies aimed at preventing
 21 diabetes and preventing diabetic complications.
 22 Q. Dr. Brancati, how much weight gain does
 23 it take to significantly increase the risk of
 24 diabetes?
 25 A. That's a good question. It depends

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

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

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

1 A. They do.

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

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

12 The other way to look at it is in
13 studies of people who are right on the verge of
14 getting diabetes and asking them to lose weight.
15 In those studies even weight loss on the order of
16 5 percent. So in someone who weighs 200 pounds,
17 that might be just 10 pounds worth of weight
18 loss, even that little bit of weight loss has a
19 big effect on lowering the risk of diabetes over
20 the next four years.

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

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

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

21 A. Yeah. Well --

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

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

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

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

5 Q. And fourfold would be 40 percent?

6 A. 400 percent.

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

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

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

18 Are you generally familiar with
19 that drug?

20 A. Yes.

21 Q. And what is it?

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

1 related to underlying psychiatric disease.

2 Q. And do you know whether it was indicated
3 for the treatment of schizophrenics and the acute
4 manic phase of bipolar disorder?

5 A. Yes, it is.

6 Q. Are there any peer-reviewed scientific
7 articles addressing the issue of whether Zyprexa
8 and other atypical antipsychotic drugs are
9 associated with an increased risk of diabetes?

10 A. Yes, very many.

11 Q. Roughly, how many are there?

12 A. I reviewed over 100.

13 Q. Okay. And how was it that you went
14 about collecting those articles for review? Was
15 it something that I gave you or any other lawyer
16 gave you, or how did you go about getting those
17 articles?

18 A. No, not -- not at all. We got them from
19 a variety of approaches. One thing that we do
20 very commonly in research is go to the web site
21 of the National Library of Medicine that allows
22 us to do very efficient electronic searches. So
23 we could put in terms like antipsychotic drugs or
24 specific names of drugs and then put in terms for
25 diabetes, ask the program to match it, and then

1 the National Library of Medicine will pull up
2 electronic copies of journals. That's how we got
3 to most of the papers.

4 I also looked at review articles on
5 the topic and dug back through the bibliographies
6 in those review articles, and then I took notes
7 at conferences given by medical experts and those
8 sorts of things.

9 Q. You said that that was how "we" got
10 those articles together. Did you have some
11 assistance in collecting articles for review?

12 A. Yeah. Part -- I did. Part of my
13 approach when I'm asked to draft a report, either
14 this type or other types for the federal
15 government, is for a variety of reasons I ask
16 some of the junior colleagues around me to help.
17 First, it gives them some experience. Second, it
18 allows me to deliver a product that's more
19 complete and -- and more -- and more on time.
20 And in situations like this, I rely on people to
21 pull articles for me, abstract information, do
22 some initial drafting, and then I look at it and
23 make sure it reflects my views before I present
24 it to the outside world.

25 Q. And is this process that you've

1 described of collecting the 100 or so scientific
2 articles for review, is that how you conduct
3 those types of reviews during the normal course
4 of your research activities?

5 A. That's exactly right. At Hopkins we
6 have a very active group that does what's called
7 systematic reviews, where we're charged by the
8 federal government with reviewing the evidence in
9 a particular area in order to write a report that
10 could help physicians or policymakers or insurers
11 set policy, and we use a very similar approach.

12 Q. Okay. And of these 100 articles that
13 you reviewed, when did they first begin to be
14 published in the scientific literature? Let me
15 back up for a second.

16 Were these articles that you
17 reviewed, were they in the peer-reviewed type of
18 journals that you described earlier?

19 A. Yes, peer reviewed.

20 Q. Did you restrict yourself to
21 peer-reviewed articles?

22 A. We did, yes.

23 Q. And why did you restrict yourself to
24 those articles?

25 A. Those are the higher quality papers.

1 The peer-reviewed papers, as I mentioned a few
2 minutes ago, are the ones that have been subject
3 to the most scrutiny, candid scrutiny by peers at
4 other institutions. So one of the rules we have
5 in academia is when you write a paper, you can
6 almost always get it published somewhere. You
7 just keep sending it around. Even if your peers
8 think the science is bad, you can find someplace
9 for it because there are plenty of journals out
10 there.

11 I don't like to rely on those
12 sources when I'm writing a report. We also don't
13 like to publish there because my colleagues at
14 Hopkins will know that we've taken the low road
15 instead of the high road, so the gold standard in
16 the field is the peer-reviewed scientific
17 journals.

18 Q. Okay. Of those 100 or so peer-reviewed
19 journal articles that you reviewed, when was it
20 that they first began to be published with
21 respect to linking Zyprexa with diabetes?

22 A. Well, really from the -- you know, mid
23 to late '90s and then through the end of 2006
24 when I wrote the report.

25 Q. Okay. And I'd like to talk about the

1 different types of scientific evidence.

2 Let me ask you this question:

3 These articles that you reviewed, do they for the
4 most part report on various types of studies that
5 were done to analyze the question of whether
6 Zyprexa is related with hyperglycemia or
7 diabetes?

8 A. Yes.

9 Q. Okay. And I presume there were also
10 some review articles that reviewed the literature
11 as well?

12 A. Yes.

13 Q. With respect to those articles that
14 talked about studies that were conducted, would
15 it be fair to say that there were probably
16 several different types of methodologies that can
17 be used to conduct such studies?

18 A. Yes.

19 Q. Okay. And do we have a chart here that
20 just sort of lists the different types of studies
21 that were done to address the question of whether
22 Zyprexa is related to diabetes?

23 A. Yes.

24 Q. There we go. Sometimes it works,
25 sometimes it doesn't.

1 This chart's entitled, Types of
2 Scientific Evidence Available to Determine
3 Whether Zyprexa Causes Diabetes, and then we have
4 listed there five different types of -- of
5 studies that were available in this area; is that
6 correct?

7 A. That's right.

8 Q. Okay. And can you just briefly describe
9 for us what type of -- what's involved in a case
10 report or a case series?

11 A. A case report is very much what it
12 sounds like. It's a case that sparked the
13 curiosity or suspicion of an individual physician
14 about an individual patient. They saw something
15 going on with that event that they thought other
16 doctors should know about and they write up that
17 case.

18 Q. Okay.

19 A. The case series is a series of those
20 kinds of cases. So, maybe when they saw the
21 first case, they were a little suspicious, but
22 they weren't really moved to write anything up,
23 to take the time to do it. But when they saw the
24 second or the third or the fourth case, they say
25 to themselves, hey, I think there's something

1 going on here. I really didn't expect it the
2 first time. Now I've seen three or four cases.
3 Now I feel motivated enough to write it up.

4 Q. And can a peer case report just standing
5 alone ever prove causation?

6 A. No, it can't. Really, no one study by
7 itself, with the exception of that hypothetical
8 long-term, randomized human experiment, ever
9 nails causality. Case reports and case series
10 more so than most, because they're anecdotal,
11 they're single episodes. But having said that,
12 it's an important part of the scientific
13 literature, because often we never get to the
14 other studies unless there's some suspicion based
15 on the keen observation of physicians, and then
16 there are elements of those studies that can add
17 to their persuasiveness depending on the nature
18 of the case report.

19 Q. Are those case report -- well, let me
20 ask this: Are there particular types of case
21 reports that can, indeed, provide evidence of
22 causality?

23 A. The type of case report or case series
24 that can be most suggestive of a potential causal
25 relationship are the ones where there's been a

1 dechallenge and/or a rechallenge. What do I mean
2 by that? The pharmacologists, my colleagues in
3 that field, people who study drugs for a living,
4 they'll consider the initial use of a drug to be
5 the challenge. Somebody goes on drug X and then
6 they get sick and that's the initial challenge.

7 Now, the dechallenge is when the
8 drug is withdrawn. So, you give someone a new
9 drug, they develop wheezing and asthma. You take
10 them off the drug. If the wheezing and asthma
11 continues, you say, well, maybe it was the drug
12 that started it, but, gee, I wonder why they
13 still have it now.

14 You get dechallenge evidence of an
15 association when they felt fine; you give the
16 drug; they get wheezing and asthma; you take the
17 drug off; wheezing and asthma gets better. Now
18 it looks like, gee, maybe it wasn't the drug,
19 because they didn't have it before; they don't
20 have it now; it was only when they were on the
21 drug.

22 Now, if you really want even
23 greater proof and the physician and the patient
24 are willing, you can try a rechallenge. So they
25 felt fine; put them on the drug, wheezing and

1 asthma; take them off the drug, wheezing and
2 asthma goes away. Then the physician and the
3 patient say, you know, I'd really like that drug.
4 It was really helping me in other ways. Are we
5 100 percent certain that it was the drug? You
6 say, okay, let's try a rechallenge. So, start
7 the drug again. If wheezing and asthma comes
8 back, you say, gee, it seems like it's got to be
9 the drug. What else could explain that kind of
10 pattern?

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

15 A. There were.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 A. That's right.

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

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

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

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

9 A. That's right.

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

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

25 And in four of the five studies we

1 drugs to put Zyprexa in context.

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

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

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

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

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

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

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

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

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

14 A. We did.

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

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

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

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

13 A. Yes.

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

16 A. Than risperidone, yes.

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

19 A. There were.

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

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

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

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

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

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

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

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

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

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

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

1 that.

2 That's why the A1C was developed.
3 This is a test that relies on an interesting and
4 incidental biochemical fact, and that is that
5 blood sugar tends to bind to the hemoglobin
6 molecule. Hemoglobin may sound vaguely familiar
7 to you. If it does, it's because it's one of the
8 most common proteins in the body. It's what
9 carries oxygen in blood. Actually the iron in
10 blood is bound to hemoglobin. That's what gives
11 blood its red color. So there's a lot of it, and
12 it circulated all throughout the body.

13 Now, what does hemoglobin have to
14 do with diabetes or sugar? Really, nothing,
15 except there's so much of it acts like an
16 incidental -- an accidental bystander, actually a
17 little bit like a sponge and it absorbs a little
18 bit of blood sugar, and a single sugar molecule
19 combined on to one sticky end of a hemoglobin.

20 In people without diabetes, about 5
21 percent of all the hemoglobin molecules
22 circulating in the blood have a sugar attached.
23 We say their hemoglobin A1C is 5 percent. That's
24 at normal levels of blood sugar. As the blood
25 sugar rises, that percentage goes up. It goes

1 from 5 to 6 percent to 7 percent, can go to 11 or
2 12 percent. Doctors compare notes, the highest
3 A1C they've ever seen. Could be 13 or 14
4 percent. Each 1 percentage of A1C represents
5 about 35 milligrams per deciliter of glucose.

6 The great thing about A1C and the
7 reason it's so widely used in practice now is
8 that it's really impervious to what happened the
9 night before or what happened the morning of the
10 test or even what happened the week before. It
11 ends up being a time average of blood sugars over
12 the life of the red blood cell. Red blood cells
13 circulate for about three months, so this is a
14 biological average of blood sugar over a period
15 of three months. So it's a much more stable
16 measurement than blood sugar, much more reliable,
17 and you can draw it in the morning after a fast.
18 You can draw it in the afternoon after a Big Mac.
19 The Big Mac won't affect it.

20 So it's very useful in studies,
21 like the studies done of antipsychotic drugs
22 because people who don't do -- researchers who
23 don't do diabetes research tend not to fuss about
24 the time of day they bring patients back for
25 their study tests. In fact, it's more convenient

1 to let people come whenever they want, 8:00 in
2 the morning, 2:00 in the afternoon, 6:00 at
3 night. It's easier to do that. Many studies
4 outside the diabetes and heart disease world do
5 that. They let people come back any time of day.

6 That creates a little bit of a
7 problem when you go back and try to figure out if
8 your medication is causing problems in terms of
9 blood sugar, because the blood sugar varies so
10 much during the day you introduce a lot of noise.
11 That's one of the inherent problems in the
12 literature around blood sugar and antipsychotic
13 drugs. There's a lot of noise introduced by the
14 fact that in many of the studies participants
15 came back at different times of day. After a
16 meal the blood sugar can be a lot higher.

17 The CATIE investigator showed a lot
18 of foresight by building in the A1C. They were
19 thinking about the hypothesis that Zyprexa and
20 other atypical antipsychotic drugs might provoke
21 hyperglycemia. They measured blood sugar, but
22 predictably they got a lot of noise in that
23 measurement. They also built in the A1C so they
24 can get a precise measurement. We don't have
25 this in many studies of hyperglycemia, but in one

1 of the best and biggest studies we do.

2 And Zyprexa raised hemoglobin A1C
3 about .4 percent. One percent is about 35
4 milligrams per deciliter; .4 percent is around 15
5 or 17 milligrams per deciliter. It turns out it
6 actually jibes pretty well with some of the other
7 studies that looked at glucose alone. So it
8 ended up being a pretty compelling result.

9 Q. Just to make sure I understand this.

10 The CATIE study which used that
11 hemoglobin A1C test found that Zyprexa users had
12 higher levels of blood glucose as compared to
13 risperidone users and for perphenazine users and
14 ziprasidone; is that correct?

15 A. Yes.

16 Q. In your view, was the use of that
17 hemoglobin A1C test in the CATIE study, was that
18 a particularly appropriate methodology to address
19 this issue of whether Zyprexa can cause
20 hyperglycemia?

21 A. I think it was -- it was a smart idea,
22 because the blood sugar levels can vary quite a
23 bit especially if people come back for visits at
24 different times of day. If you get people back
25 at exactly the right time and you do a fasting

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

7 Q. And is the trade name for risperidone
8 Risperdal?

9 A. Yes.

10 Q. Is the trade name for ziprasidone
11 Geodon?

12 A. Yes.

13 Q. Do you know the trade name for
14 perphenazine?

15 A. I forget offhand.

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

17
18 We talked earlier about the
19 Bradford-Hill criteria and how epidemiologists
20 use those criteria to evaluate whether a
21 relationship is causal. You've now told us the
22 findings -- or summarized the findings from these
23 various different types of evidence contained in
24 these different types of studies.

25 What I'd like for you to do now for

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

7 Will you do that for us?

8 A. Sure.

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

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

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

20 THE COURT: Okay.

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

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

25 THE COURT: Thank you.

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

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

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

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

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

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

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

4 Biological gradient, I lead off
5 saying I didn't really see great evidence there
6 in terms of duration of dose or the amount of
7 Zyprexa taken, so I think that's a weak spot.
8 Plausibility; I'd say -- we didn't
9 go after animal studies, but the references we
10 saw in the reviews, I think, were consistent
11 enough that the results were biologically
12 plausible. And I think the biggest factor here
13 for me was the very strong association between
14 Zyprexa and substantial weight gain. Weight
15 gain, as I said a few moments ago, is the leading
16 risk factor, the single strongest risk factor for
17 the occurrence of type 2 diabetes.

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

25 Q. Can I pause there and show another slide

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

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

20 Q. This was just over ten weeks, correct?

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

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

5 Can you describe for us what this
6 chart shows?

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

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

25 And when Allison and colleagues did

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

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

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

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

18 A. That's correct.

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

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

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

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

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

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

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

25 A. Remember, analogy has to do with when I

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

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

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

18 A. Similar molecular structure.

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

23 A. Exactly.

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

1 leading questions. I just raise that as an
2 objection.

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

9 MR. KANTRA: Sure. Thank you, sir.

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

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

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

1 unpredictable complication called agranular
2 cytosis.

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

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

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

25 But having said that, we -- we

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

10 Q. Thank you, Dr. Brancati.

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

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

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

22 Q. Do you have an opinion as to whether
23 Zyprexa use increases the risk of developing type
24 2 diabetes compared to people with severe mental
25 illness who use antipsychotic drugs other than

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

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

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

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

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

22 A. Yes, it is.

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

1 Zyprexa?

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

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

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

15 A. I do think it is, yes.

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

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

21 Q. Let me be more specific than that.

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

1 A. Yes, that's right.

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

6 A. That's right.

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

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

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

14 A. Yes.

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

20 A. Yes, there were. There were several.
21 There was the American Diabetes Association.
22 There was the American Psychiatric Association.
23 There was the North American Association for the
24 Study of Obesity, and there was the American
25 Association of Clinical Endocrinology.

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

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

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

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

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

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

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

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

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

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

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

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

17 A. Yes, very much so.

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

21 A. It was several days, I believe.

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

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

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

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

7 A. Yes, he was.

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

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

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

20 A. Sure.

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

23 A. He did, yes.

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

1 this trial?
 2 A. I believe they are.
 3 Q. Were there also presentations made by
 4 FDA representatives at that conference?
 5 A. Yes.
 6 Q. And were there representatives of drug
 7 companies who made presentations at that
 8 conference?
 9 A. I believe there were, yes.
 10 Q. One of which was Ms. Cavazzoni; is that
 11 correct?
 12 A. Yes.
 13 Q. I shouldn't misspeak. It was
 14 Dr. Cavazzoni, correct?
 15 A. (Witness nods head.)
 16 THE COURT: You've got to answer
 17 out loud.
 18 THE WITNESS: Yes.
 19 Q. (BY MR. SUGGS) After hearing all of
 20 that evidence and after reviewing all those
 21 papers and after deliberating for three days,
 22 this panel of experts essentially came up with
 23 these findings; is that correct?
 24 A. That's correct.
 25 Q. If I can direct your attention to some

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

1 Q. And is that consistent with your
 2 opinions?
 3 A. Yes.
 4 Q. I'm going to direct your attention now,
 5 sir, to the summary section of the article. And
 6 at the beginning of that summary, do they talk
 7 about a constellation of adverse effects?
 8 A. Yes, they do.
 9 Q. And what are the three that they --
 10 three adverse effects that are discussed in this
 11 summary?
 12 A. They mention increased risk for obesity,
 13 diabetes and dyslipidemia.
 14 Q. And then down at the bottom in the
 15 summary, this panel of experts reported that,
 16 quote, These three adverse conditions are closely
 17 linked and their preference appears to differ
 18 depending on the SGA used. Clozapine and
 19 olanzapine are associated with the greatest
 20 weight gain and highest occurrence of diabetes
 21 and dyslipidemia. Risperidone and quetiapine
 22 appear to have intermediate effects.
 23 Aripiprazole and ziprasidone are associated with
 24 little or no significant weight gain or
 25 diabetes or dyslipidemia, although they have not

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

1 took our break.

2 (Discussion off the record.)

3 Q. (BY MR. SUGGS) One point Mr. Allen has
4 suggested I go into and I agree. We talked about
5 the number of the cases and the case reports. I
6 believe you said that there were hundreds of
7 reports to FDA of -- of diabetes-related events
8 with respect to Zyprexa; is that correct?

9 A. That's correct.

10 Q. Okay. In the -- are doctors required to
11 report adverse events to FDA?

12 A. In theory, they -- they are. Often --
13 they don't. Many of them go unreported.

14 Q. And is it generally regarded in the
15 field of epidemiology and in the area of
16 pharmacovigilance that the number of adverse
17 events reported is only the tip of the iceberg?

18 A. Yes, it could be only the tip of the
19 iceberg.

20 Q. I realize it's one of those things you
21 don't know what you don't know, but have there
22 been estimates as to what fraction or percentage
23 of true adverse events ever actually get reported
24 to FDA?

25 A. In general, that's something I don't

1 I don't know what the
2 cross-examination is going to be like, but I want
3 to be sure we have time if the jurors have any
4 questions as well with this witness. So, like I
5 said, if it's only shortly going past 1:30 so
6 that the witness can be completely done, I'd
7 rather let him get completely done, but I'm not
8 going to go beyond five or ten minutes. If it
9 turns out we need more time than that, we'll just
10 end at 1:30.

11 Mr. -- and I can't reading my
12 handwriting -- is it Kantra?

13 MR. KANTRA: Kantra, yes.

14 MR. SUGGS: Excuse me, Your Honor.
15 I ran off with the witness' copy of his report,
16 if I could just hand it to him.

17 THE COURT: Please.

18 MR. SUGGS: I believe Dr. Brancati
19 found the date of the CATIE study that you were
20 asking about.

21 THE COURT: Okay. Dr. Brancati,
22 what's the date of the CATIE study?

23 THE WITNESS: September, '05.

24 THE COURT: Okay. Thank you.

25 VENIREPERSON: Your Honor, I've got

1 know.

2 Q. Okay.

3 MR. SUGGS: Very good. I have no
4 further questions at this time, Your Honor.

5 THE COURT: Thank you. Ladies and
6 gentlemen of the jury, we're going to take our
7 second break of the morning, and we'll take about
8 a 15-minute break and then we'll begin with the
9 cross-examination of the doctor.

10 We'll be in recess.

11 (Jury out.)

12 (Break.)

13 THE COURT: We're back on the
14 record and all members of the jury are present.

15 I'm advised that one of the jurors
16 just asked the clerk whether we're getting out of
17 here at 1:30 today, so this is what I'm going to
18 tell everybody. If -- if the witness, including
19 questions from the jurors, needs five or ten
20 minutes to finish up and be done and that would
21 be the end of it, I'll give the extra five or ten
22 minutes so that we can finish up the witness. If
23 it's going to be more than five or ten minutes,
24 we're going to stop at 1:30 and we'll come back
25 tomorrow with the witness.

1 a brief question, if I could. The study was done
2 in '05, and you asked when it was published?

3 THE COURT: I asked when it was
4 published, that's correct. And my understanding
5 is that it was published in '05.

6 THE WITNESS: Yes.

7 THE COURT: Go ahead.

8 CROSS-EXAMINATION

9 Q. (BY MR. KANTRA) Good afternoon,
10 Dr. Brancati.

11 A. Hi.

12 Q. You mentioned a study during the course
13 of your testimony called the look-ahead study.

14 A. Yes.

15 Q. I wondered if you could just tell us a
16 little bit more about what that study is designed
17 to do?

18 A. Sure. It's a randomized-control, a
19 human experiment designed to determine the
20 long-term health benefits of voluntary weight
21 loss in people who have diabetes.

22 Q. And what is the thinking in terms of
23 what those interventions might accomplish?

24 A. The thinking is that weight loss might
25 reduce the subsequent risk of heart attack in

1 people with diabetes.
 2 Q. Any other benefits that might accrue?
 3 A. It's looking at a whole range of
 4 possible outcomes. Mortality, other forms of
 5 heart disease, peripheral vascular disease.
 6 Q. Okay. Have you consulted at all for
 7 FDA?
 8 A. No.
 9 Q. You testified about a -- an atypical
 10 antipsychotic other than clozapine -- or other
 11 than Zyprexa which is called clozapine, right?
 12 A. Yes.
 13 Q. And you mentioned that they are
 14 structurally similar, but also recognize that
 15 they are different compounds, right?
 16 A. Yes.
 17 Q. If you were prescribed Zyprexa, you
 18 couldn't fill it with clozapine, correct?
 19 A. Correct.
 20 Q. And you mentioned that there was a fatal
 21 side effect associated with clozapine, right?
 22 A. Yes.
 23 Q. And you called that agranular cytosis?
 24 A. Yes.
 25 Q. Can you tell the jury what that is?

1 A. Sure. The blood is made up of many
 2 types of cells. Red cells are the ones most
 3 familiar to us, but then there are white cells,
 4 as well, the ones involved in fighting infection.
 5 There are a variety of different flavors of the
 6 white blood cells, and some of them are granular
 7 sites and they're important in fighting
 8 infection. The condition of agranular cytosis is
 9 a sudden loss of those cells, and it can be a
 10 devastating complication because it can
 11 predispose to serious infection.
 12 Q. And ultimately can lead to death?
 13 A. Yes.
 14 Q. Because it's a serious side effect, one
 15 of the things that's required is monitoring,
 16 correct?
 17 A. Correct.
 18 Q. And the way that they monitor for
 19 agranular cytosis is by drawing blood, right?
 20 A. Yes.
 21 Q. In much the same way that you described
 22 blood monitoring earlier today, right?
 23 A. Yes.
 24 Q. You told us earlier that you had
 25 evaluated the published literature as the basis

1 for forming your opinions, right?
 2 A. Correct.
 3 Q. I take it from that that you did not
 4 consider or rely upon any submissions that Lilly
 5 made to FDA in forming your opinions in this
 6 matter?
 7 A. That's right, I did not rely on those
 8 sources.
 9 Q. So I take it from that, then, that you
 10 didn't consider a submission that Lilly made in
 11 July of 2000 with respect to an analysis of about
 12 4,000 clinical trial patients; is that right?
 13 A. That's right.
 14 Q. And I would assume, then, from your
 15 answer that you would have not considered a
 16 submission that Lilly made in May of 2001 that
 17 included a second clinical trial analysis that
 18 evaluated diabetes risk in patients treated with
 19 Zyprexa; is that right?
 20 A. That's right.
 21 Q. And I would assume as well that in March
 22 of 2003, the Lilly submission that was made then
 23 that evaluated diabetes-related adverse events
 24 after 9 million patient exposures, you wouldn't
 25 have reviewed that as well?

1 A. That's correct.
 2 Q. And with respect to a Lilly June, 2003
 3 FDA submission regarding patients with
 4 preexisting diabetes and whether their condition
 5 worsened on Zyprexa, you wouldn't have reviewed
 6 that either?
 7 A. That's right.
 8 Q. I want to take a step back to the May,
 9 2001 submission. And, in particular, I want to
 10 ask you a couple of questions around that.
 11 Do you know David Allison?
 12 A. Yes, I do.
 13 Q. Okay. Dr. Allison is a witness for the
 14 State of Alaska in this litigation?
 15 A. Yes.
 16 Q. You respect him and the work that he
 17 does?
 18 A. Yes.
 19 Q. And you consulted with him in preparing
 20 your report in this matter, didn't you?
 21 A. Yes, on one occasion.
 22 Q. You're aware that Lilly invited
 23 Dr. Allison in to critique its clinical trials
 24 back in the 2000/2001 time frame?
 25 A. It sounds right, but I don't think we

1 discussed it.

2 Q. You didn't -- so he didn't tell you what
3 the results of his analysis were?

4 A. No.

5 Q. You described diabetes as a
6 condition which is quite prevalent in our society
7 today, right?

8 A. Yes.

9 Q. From 1980 through 2005, the number of
10 people with diabetes in this country tripled
11 approximately?

12 A. Yes.

13 Q. Sound about right? From about 5 and a
14 half million to more than 16 million?

15 A. Yes.

16 Q. In 2005 alone, there were about one and
17 a half million new cases of diabetes? Does that
18 sound right?

19 A. Yes.

20 Q. And general estimates for how common
21 diabetes is in the general population of the
22 United States at least is about 7 percent,
23 roughly?

24 A. Roughly, yes.

25 Q. Okay. And that means that approximately

1 20 million people in this country have diabetes?

2 A. Yes.

3 Q. That would be about 1 out of every 14
4 people?

5 A. Yes.

6 Q. And of those, about 6 million people
7 are -- have undiagnosed diabetes, right?

8 A. Yes.

9 Q. And what that means is that they don't
10 even know that they have diabetes?

11 A. That's correct.

12 Q. And that may be due in part to the fact
13 that diabetes in general is a slow-moving
14 condition, right?

15 A. Yes, I agree.

16 Q. And as you said, it's not always
17 accompanied by symptoms when it first presents?

18 A. Correct, yeah.

19 Q. And that's consistent with the fact that
20 there are often delays in the time that it takes
21 from onset of diabetes to the time of actual
22 diagnosis?

23 A. That's right.

24 Q. And you've estimated that that's
25 somewhere between -- can be between 2 and 7

1 years?

2 A. Yes.

3 Q. You're aware that approximately 23
4 million people have taken Zyprexa?

5 A. That sounds right, yes.

6 Q. And since diabetes is a relatively
7 common medical condition, you would expect that
8 just by chance alone you would expect some people
9 to develop diabetes during the course of their
10 treatment with Zyprexa?

11 A. Yes.

12 Q. One of the other things that Mr. Suggs
13 asked you about during the course of your
14 testimony was risk factors for diabetes.

15 A. Yes.

16 Q. And as someone who is familiar with the
17 disease state of diabetes, you know that there
18 are a number of different risk factors, right?

19 A. Yes.

20 Q. And you talked about weight gain as
21 being one of those?

22 A. Yes.

23 Q. Obesity, overweight, right?

24 A. Yes.

25 Q. But there are also factors, for example,

1 like physical inactivity, right?

2 A. Right.

3 Q. And as you mentioned, family history
4 would be a risk factor for diabetes, right?

5 A. Yes.

6 Q. And being over the age of 45 is a risk
7 factor for diabetes?

8 A. Unfortunately, yes.

9 Q. And as you said, various ethnic groups
10 in our country have higher risks than others for
11 developing diabetes as well?

12 A. Yes.

13 Q. All those would form the rubric of what
14 we are describing as risk factors, right?

15 A. Correct.

16 Q. Let's talk for a minute specifically
17 about obesity and overweight. And as you
18 described it, this is probably one of the most
19 well-recognized risk factors for diabetes, isn't
20 it?

21 A. Yes.

22 Q. And it's been known for years that
23 that's a risk factor for diabetes; isn't that
24 right?

25 A. Correct.

1 Q. Something you learned about as part of
 2 your basic medical school training?
 3 A. Exactly, yes.
 4 Q. Doctors frequently tell patients that
 5 they need to watch their weight, right?
 6 A. Yes.
 7 Q. And there are extensive efforts, as you
 8 mentioned, to educate the public about weight
 9 gain as well?
 10 A. Yes.
 11 Q. And as you suggested, the medical
 12 community has focused on this question
 13 specifically within the context of atypical
 14 antipsychotics; isn't that right?
 15 A. Yes.
 16 Q. And Dr. Allison published that chart
 17 that you put up on that screen, right?
 18 A. Yes.
 19 Q. And that was published nine years ago,
 20 wasn't it?
 21 A. Yes.
 22 Q. Almost 2 out of every 3 adults in the
 23 United States are either overweight or obese;
 24 isn't that right?
 25 A. Yes.

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

1 levels within the normal range, right?
 2 A. Yes.
 3 Q. Does it sound about right that a quarter
 4 or 25 percent of the American public has insulin
 5 resistance?
 6 A. I'd say roughly, yes.
 7 Q. Again, even though 25 percent of the
 8 U.S. population has insulin resistance, 25
 9 percent of the population is not diabetic, right?
 10 A. Correct.
 11 Q. Again, many people who have insulin
 12 resistance don't develop diabetes?
 13 A. Correct.
 14 Q. You also described something, I believe,
 15 as impaired fasting glucose or impaired glucose
 16 tolerance. You recall that?
 17 A. Yes.
 18 Q. Sometimes that's call prediabetes?
 19 A. Yes.
 20 Q. Another term. And the American Diabetes
 21 Association recognizes that as a risk factor for
 22 diabetes as well, doesn't it?
 23 A. Correct.
 24 Q. Represents a condition where somebody
 25 has blood sugar problems, but they haven't

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

1 different epidemiological studies relating to
2 diabetes?
3 A. Correct.
4 Q. And if you were asked to design a study
5 that was intended to look at the question of
6 whether or not an atypical antipsychotic
7 medication or any medication for that matter was
8 leading to the development of diabetes, it would
9 be important for you to know the extent to which
10 risk factors were distributed among the patients
11 who were in the study, wouldn't it?
12 A. Yes.
13 Q. And that's because without that sort of
14 information, it would be difficult to make
15 reliable assessments about whether any effects
16 that might be observed were due to effects from
17 the medication or to differences among the people
18 who were actually being treated?
19 A. Correct.
20 Q. So if someone were designing this kind
21 of a study that was intended to actually look at
22 the question of whether medication causes
23 diabetes, it would be important to do your best
24 to make sure that the risk factors were as
25 balanced as they could be among the various

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

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

1 A. -- small groups. The experimental
2 studies are going on in realtime as well, but the
3 cohort studies and the case-control studies, the
4 cross-sectional studies, yes, were generally done
5 with existing databases where the dust had
6 settled and it was a matter of the epidemiologist
7 looking for patterns in the existing data.
8 Q. Are you familiar with a 2007 article by
9 Leslie Sitron that evaluated risk factors within
10 the context of atypical antipsychotic medications
11 and emergence of diabetes?
12 A. I didn't prepare for the report anything
13 beyond --
14 Q. 2006?
15 A. -- yeah, 2006.
16 Q. Conventional medical wisdom has it that
17 it takes years for the insulin-resistance
18 associated with weight gain to contribute to the
19 development of defective insulin production,
20 right?
21 A. Yes.
22 Q. And defective insulin production at its
23 heart is what diabetes is all about, right?
24 A. Yes.
25 Q. And, in fact, you've published an

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

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

1 A. No, I'm good.
 2 Q. If you look at the article, this is an
 3 article which is entitled Body Weight Patterns
 4 from 20 to 49 Years of Age and Subsequent Risk
 5 for Diabetes Mellitus?
 6 A. Yes.
 7 Q. And as you mentioned, this is a Johns
 8 Hopkins precursor study, right?
 9 A. Yes.
 10 Q. This is an article where you are the
 11 lead author?
 12 A. Yes.
 13 Q. And it was published in a medical
 14 journal known as The Archives of Internal
 15 Medicine?
 16 A. Yes.
 17 Q. This is considered to be a peer-reviewed
 18 article, isn't it?
 19 A. We were very proud of this one.
 20 Q. And you submitted it with the belief
 21 that you were making an important contribution
 22 that others could learn from?
 23 A. Yes.
 24 Q. And if I could turn your attention to
 25 that last paragraph on the last page, and if you

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

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

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

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

17 A. No.

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

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

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

25 A. No.

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

4 A. Yes.

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

7 A. Yes, I am.

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

10 A. Yes.

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

13 A. No.

14 Q. Have you ever been?

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

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

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

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

25 A. Yes.

1 Q. Where the risk factors are listed?

2 A. Yes.

3 Q. For diabetes?

4 A. Yes.

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

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

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

13 A. Correct.

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

17 A. Yes.

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

22 A. That's correct.

23 MR. KANTRA: Go ahead and pull up
24 2000 -- EL2001. And if we could go -- I think
25 it's the fourth page of that document.

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

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

8 A. Yes.

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

10 A. Yes.

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

15 A. That's right.

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

21 A. Yes.

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

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

1 the treatment emergent diabetes risk for these
 2 drugs is wholly or in part due to
 3 treatment-emergent weight gain. And it goes on
 4 to say that although weight gain is widely
 5 recognized as a risk factor for diabetes in the
 6 general population, the clinical trial -- and
 7 that's another way of saying the experimental
 8 evidence; is that right --
 9 A. Yes.
 10 Q. -- consistent with what you said?
 11 And the epidemiological evidence,
 12 which is the cohort studies and the case-control
 13 studies that you talked about?
 14 A. Yes.
 15 Q. Have not shown a direct link between
 16 these treatment-emergent side effects.
 17 A. Correct.
 18 Q. That's what FDA's view was in 2004?
 19 A. Yes.
 20 Q. When you were talking with Mr. Suggs
 21 about your background and what you do --
 22 A. Yes.
 23 Q. -- one of the things that you mentioned
 24 was that you teach, right?
 25 A. Yes.

1 Q. And among other things, what I
 2 understand is that you teach students who are
 3 learning about epidemiology?
 4 A. Yes.
 5 Q. And one of the things that you do is you
 6 help to educate them about this -- how we look at
 7 evidence around the issue of causation, right?
 8 A. Yes.
 9 Q. And in helping to teach them about this
 10 evidence relating to causation, you help teach
 11 them about the same hierarchy of evidence that
 12 was up on the screen earlier, don't you?
 13 A. Yes.
 14 Q. And that hierarchy of evidence would run
 15 from the case reports that you talked about
 16 initially, up through these observational
 17 epidemiological studies, to clinical trials or
 18 experimental trials at the top?
 19 A. Yes.
 20 Q. Okay. And you had mentioned a couple of
 21 times that sometimes work is done with animals to
 22 evaluate safety-related issues, right?
 23 A. Correct.
 24 Q. And those types of studies are helpful
 25 for identifying ideas for future studies in

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

1 A. Correct.
 2 Q. Okay. With respect to these kinds of
 3 studies, what we don't have in contrast to the
 4 experimental studies or the clinical trials that
 5 you've talked about, is what's called a control
 6 group, right?
 7 A. That's right.
 8 Q. And so what we don't know with respect
 9 to either the dechallenge cases or the
 10 rechallenge cases, for that matter, is how many
 11 patients were taken off drug having developed it
 12 without an improvement, right?
 13 A. Yes.
 14 Q. Similarly, what we don't know is how
 15 many patients were put back on drug, but then
 16 didn't redevelop the event?
 17 A. Right.
 18 Q. That's just information that we don't
 19 have the benefit of?
 20 A. That's right.
 21 Q. And one of the reasons why it's helpful
 22 to have information like what I've just
 23 described, information about numbers of patients
 24 who didn't develop a particular adverse event
 25 after dechallenge or rechallenge, is that it

1 helps us to identify a rate at which something is
 2 occurring, right?
 3 A. Correct.
 4 Q. And in identifying what that rate is, it
 5 helps us understand whether we're seeing
 6 something that is in excess of what we would
 7 expect to see or consistent with what we would
 8 expect to see?
 9 A. That's right.
 10 Q. With dechallenge and rechallenge cases,
 11 we don't always know, many times we don't know,
 12 whether, in fact, there have been changes in a
 13 patient's lifestyle or medications or medical
 14 history that may affect the outcome of it?
 15 A. Could be, yes.
 16 Q. Put differently, perhaps, the reports
 17 that -- that are published in the literature or
 18 submitted to FDA depend, in part, on the quality
 19 and the knowledge and experience of the physician
 20 who's actually making the report?
 21 A. Yes.
 22 Q. And how familiar they are with the
 23 relevant issues?
 24 A. Yes.
 25 Q. And even within the context of a person

1 who develops diabetes and then is taken off drug
 2 with improvement after that point, there is what
 3 is known as a spontaneous remission sometimes,
 4 right?
 5 A. Rare.
 6 Q. But it happens?
 7 A. Yes, I -- I've not seen it in my
 8 practice, but it could happen.
 9 Q. But you're aware of it?
 10 A. Yes.
 11 Q. It's been reported in the literature?
 12 A. Yes.
 13 Q. And you would agree with me that these
 14 individual case reports that we've been talking
 15 about are different in kind from the clinical
 16 trials that you've described in this -- in this
 17 hierarchy of evidence, right?
 18 A. Yes.
 19 Q. And they would be very different in
 20 terms of the quality of the evidence from studies
 21 that are designed specifically to look at the
 22 question of whether there is a mechanism by which
 23 a drug can result in causing diabetes?
 24 A. Yes.
 25 Q. If we look back at the case reports that

1 have been published, what I recall from your
 2 testimony is that you said that the first case
 3 reports relating to Zyprexa and cases of diabetes
 4 were approximately 10 years ago, right?
 5 A. Yes.
 6 Q. You said mid-'90s, I believe?
 7 A. Yes.
 8 Q. And I believe what you told us was that
 9 case reports provide a basis, again, for
 10 generating ideas, raising awareness of
 11 physicians, alerting them to potential issues
 12 that they might need to pay attention to?
 13 A. Yes, in general. Occasionally they're
 14 so persuasive that they constitute evidence in
 15 themselves, for example, a very unusual type of
 16 complication that would otherwise rarely or never
 17 occur. With diabetes, as you pointed out, it's
 18 common enough in everyday practice that it's hard
 19 to tell for certain from case reports alone.
 20 Q. You would agree with me that between
 21 1998 when the first case report for Zyprexa was
 22 published, and the spring of 2002, the evidence
 23 that was available with respect to the issue of
 24 whether or not Zyprexa could cause diabetes was
 25 limited to case reports?

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

1 so you understand what I'm asking --
 2 MR. SUGGS: Your Honor, can we have
 3 the witness be allowed to finish his answer?
 4 THE COURT: I don't think -- were
 5 you finished or --
 6 THE WITNESS: Yeah.
 7 THE COURT: Okay. Go ahead.
 8 Q. (BY MR. KANTRA) The article or the
 9 analysis that you've referenced in regards to
 10 those -- those various case reports, separate and
 11 apart from an analysis of case reports, if we're
 12 talking about cross-sectional studies, cohort
 13 studies, those sorts of things within the
 14 epidemiological sphere, you're not aware of any
 15 epidemiology studies relating to Zyprexa and
 16 diabetes that were published before the spring of
 17 2002; isn't that right?
 18 A. That sounds right. No, the vast
 19 majority were after that time. I can't recall
 20 offhand whether there were any before that time.
 21 Q. Sitting here today, you don't -- you
 22 don't remember any?
 23 A. No.
 24 Q. And you've not offered any sort of
 25 opinion that the literature as it existed as of

1 2002 was sufficient to support the conclusion
 2 that Zyprexa causes diabetes, right?
 3 A. Right, the published literature which is
 4 what I review, yeah.
 5 Q. Published literature, exactly.
 6 Let's talk for a minute about
 7 epidemiology studies as you've defined them. The
 8 limitations of these kinds of studies, most
 9 precisely or perhaps most importantly relate to
 10 the issue of randomization, right?
 11 A. I'm sorry? Could you restate that?
 12 Q. Let me phrase it again.
 13 As you think about the difference
 14 between what you call these experimental studies
 15 or clinical trials --
 16 A. Yes.
 17 Q. -- and these database studies or these
 18 case-control cohort studies?
 19 A. Observational epidemiological study.
 20 Q. Observational epidemiological studies.
 21 If we're thinking about the contrast between
 22 those two things, one of the most important
 23 distinctions is the fact that the experimental
 24 studies or the clinical trials have the benefit
 25 of randomization, whereas the observational

1 epidemiological studies do not, right?
 2 A. Exactly.
 3 Q. Okay. And randomization refers to the
 4 random assignment of patients to different
 5 treatment groups, right?
 6 A. That's correct.
 7 Q. And I think you described it as patients
 8 are assigned, essentially, on the flip of a coin,
 9 right?
 10 A. That's right.
 11 Q. And the benefit of doing it that way, as
 12 we talked about earlier, is the fact that you
 13 want to make sure that as much as possible people
 14 are similarly situated in the two treatment
 15 groups so that you can assess whether or not an
 16 effect is the result of a medication or something
 17 else?
 18 A. That's right.
 19 Q. And without randomization, then,
 20 scientists who are studying the risk of whether
 21 diabetes occurs in patients on certain
 22 medications at higher rates can't be sure of
 23 whether they -- the patients were comparable with
 24 respect to their baseline risk factors for
 25 diabetes?

1 A. That's right.
 2 Q. Put differently, scientists can't be
 3 sure that they're dealing with a level playing
 4 field?
 5 A. That's correct.
 6 Q. Okay. And among other things, the
 7 absence of randomization in observational
 8 epidemiological studies is one of the reasons why
 9 an assessment of causation requires a look across
 10 all of the data, including the experimental
 11 studies, right?
 12 A. Yes.
 13 Q. You wouldn't want to limit yourself to
 14 just one bucket of evidence, right?
 15 A. That's right, although, as I pointed out
 16 with the smoking example, sometimes experimental
 17 data in humans is hard to come by. Sometimes we
 18 do put all our eggs in the observational basket.
 19 But, in general, yes, when we can, we like to
 20 have experimental evidence as well.
 21 Q. And here, certainly you didn't limit
 22 your review of the evidence just to the
 23 epidemiological studies, right?
 24 A. Right.
 25 Q. You looked beyond that to the

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

1 isn't that right?
 2 A. That's right.
 3 Q. One way to evaluate whether or not
 4 diabetes has occurred is to look at various
 5 thresholds or cutoff points, right?
 6 A. Cutoff points of glucose you mean?
 7 Q. Right. Exactly.
 8 A. Yes.
 9 Q. So, for example, when you spoke earlier
 10 about the way in which diabetes is diagnosed, one
 11 of the things you said is that if it's a random
 12 blood sugar level above 200 with symptoms, that
 13 would support a diagnosis of diabetes?
 14 A. That's right.
 15 Q. Similarly, if you have a fasting blood
 16 glucose level that is 126 or higher, that would
 17 be another basis for making a diagnosis of
 18 diabetes?
 19 A. That's right.
 20 Q. When I say thresholds, I'm referring to
 21 those kinds of cut points and, similarly, one
 22 could also look at prediabetes as a category of
 23 cases, right?
 24 A. Yes.
 25 Q. So there we'd be interested in

1 identifying patients, for example, if they were
 2 fasting, had values between 100 and 125, right?
 3 A. Yes.
 4 Q. And so if we're interested in seeing
 5 outcomes, whether it's people with prediabetes or
 6 diabetes, one way to evaluate that is to look at
 7 these categorical cut points, these significant
 8 clinical thresholds?
 9 A. Yes.
 10 Q. Okay. Another way that scientists can
 11 go about evaluating whether or not somebody in a
 12 particular analysis might have diabetes is to
 13 look at the question of whether they're actually
 14 being treated with medication for diabetes?
 15 A. That's correct.
 16 Q. So, for example, if someone is being
 17 treated with insulin, that might be something
 18 that would be of interest?
 19 A. Yes.
 20 Q. Or what they call hypoglycemic
 21 medication?
 22 A. Yes.
 23 Q. Something which lowers the blood sugar
 24 level?
 25 A. Yes.

1 Q. That would be another way, an acceptable
2 way, a recognized way of looking at whether or
3 not someone had diabetes?

4 A. Yes.

5 Q. And then there's also what is sometimes
6 referred to as a continuous analysis?

7 A. Yes.

8 Q. That would be equivalent to what is
9 called sometimes an average change analysis,
10 right?

11 A. Uh-huh, yes.

12 Q. Meaning that -- put differently, the
13 question is, on average, how -- how much do
14 patients' blood sugar levels go up while they're
15 on a particular medication?

16 A. That's right.

17 Q. And that was one of the things that you
18 talked about with respect to the CATIE study,
19 right?

20 A. Yes.

21 Q. One of the things you noted in there was
22 that there were increases in blood glucose
23 levels?

24 A. Yes.

25 Q. And then you talked about the hemoglobin

1 regard, the human experiments, the trials are at
2 the top of the pyramid.

3 The trouble is, and I think we see
4 it in the CATIE study, is that trials are hard to
5 mount in large numbers for long periods of time.
6 So frequently evidence we have from experiments
7 or trials is limited in time. Might be only
8 weeks or months. When you go into a study with a
9 time frame of only weeks or months, it may not be
10 reasonable to pin your hypothesis on the
11 development of a condition like diabetes or heart
12 disease. In those settings, even though we look
13 at all three end-points for information, my sense
14 going into the study, just reading about the
15 design before reading about the results, was that
16 the most precise continuous measures would be the
17 most informative.

18 Q. And that's actually an interesting
19 point, because there are studies, and I believe
20 you mentioned this as well during your direct
21 testimony, that if we look at continuous measures
22 or these average change measures, you're aware
23 that within the context of clinical trials that
24 compare Zyprexa with other atypical
25 antipsychotics, there are studies that compare,

1 A1C's a little bit?

2 A. Yes.

3 Q. And you recalled that in that study as
4 well they also looked at whether or not there
5 were significant differences in patients who were
6 treated with new antidiabetic medications?

7 A. Yes.

8 Q. And by that measurement they didn't
9 actually find a significance difference among the
10 treatment groups?

11 A. I think that's right, yes.

12 Q. And all of these three measurements,
13 whether we talk about these clinical thresholds,
14 this categorical analysis they're sometimes
15 called, the measurement using initiation of new
16 antidiabetic medications, or this sort of average
17 change analysis, all three of these give us
18 important and complimentary information, don't
19 they?

20 A. In general, yes, but your question
21 points to one -- one key consideration. That is,
22 going into a trial -- you rightly pointed out
23 that the experiments give the strongest type of
24 evidence because of their ability to balance
25 factors across different groups. So in that

1 for example, Zyprexa with Geodon in a direct sort
2 of head-to-head comparison.

3 Are you familiar with those
4 studies?

5 A. Yes.

6 Q. And you're familiar with the fact that
7 there are studies out there that made that direct
8 comparison between those two medications and did
9 not find statistically significant differences in
10 these average glucose levels?

11 A. Especially in some of the shorter-term
12 studies, but, yes.

13 Q. And, indeed, in studies that went up to
14 six months?

15 A. Yes.

16 Q. And you're aware of studies that
17 compared Zyprexa with this newer agent, Abilify,
18 right?

19 A. Yes.

20 Q. Which is also call aripiprazole in some
21 of your slides, I believe?

22 A. Yes.

23 Q. And you're aware that there as well,
24 there is literature which suggests that the
25 increase in average blood sugar levels is not

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

1 A. Yes.
 2 Q. And a clamp study is a study which is,
 3 as we talked at the beginning, there are things
 4 that are called mechanistic studies, right?
 5 A. Yes.
 6 Q. And those are studies that are done to
 7 help evaluate whether there is an explanation by
 8 which a particular drug might lead to the
 9 development of an outcome like diabetes?
 10 A. Yes.
 11 Q. Right?
 12 And they can measure it in two
 13 different ways, maybe more, but at least two that
 14 we know of. One is to look at the question of,
 15 does administering a drug within a clinical trial
 16 or experimental setting lead to a situation where
 17 the drug is directly injuring the pancreas such
 18 that it can't produce insulin?
 19 A. Yes.
 20 Q. And that is called a hyperglycemic clamp
 21 study, isn't it?
 22 A. Yes.
 23 Q. Then there's a second study that can be
 24 done as well, and that's a study that looks at
 25 this question of insulin resistance that we

1 talked about earlier?
 2 A. Yes.
 3 Q. And that's sometimes referred to as a
 4 euglycemic clamp study, isn't it?
 5 A. Yes.
 6 Q. What's done in those kinds of studies is
 7 to ask the question of whether, again, in an
 8 experimental kind of setting there was an effect
 9 of the drug such that people's insulin resistance
 10 actually got worse as a result of taking the
 11 drug?
 12 A. Yes.
 13 Q. And you're familiar with the fact that
 14 there were two clinical trials that Lilly
 15 conducted that looked at those issues?
 16 A. Yes.
 17 Q. And those studies would fall into the
 18 bucket of evidence that you described as being
 19 experimental, right?
 20 A. Yes.
 21 Q. And the results of those studies, each
 22 of them, found that there was no evidence of a
 23 direct effect either on insulin production,
 24 right, or increasing insulin resistance?
 25 A. I think that's right, and my

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

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

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

9 Q. And you don't see it.

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

12 THE COURT: Sure.

13 (Discussion off the record.)

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

16 THE COURT: Mr. Suggs.

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

19 THE COURT: Sure.

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

25 MR. KANTRA: That was 2004. I'm

1 sorry.

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

10 THE COURT: Again, you're certainly
11 free to bring that out through other witnesses
12 and stuff, but the purpose of this had to do with
13 the limits of the witness' testimony and his
14 report. His answer to that question was very
15 clearly that he hadn't looked at anything past
16 2006, so if you're making a motion to ask
17 questions based on them opening the door, I'll
18 deny that motion.

19 MR. SUGGS: Okay.

20 (End bench conference.)

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

23 THE COURT: You may.

24 (Discussion off the record.)

25 MR. SUGGS: Dr. Brancati, I just

1 have a few questions.

2 REDIRECT EXAMINATION

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

5 A. Yes.

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

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

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

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

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

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

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

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

19 Q. Does Zyprexa cause diabetes,
20 Dr. Brancati?

21 A. I believe it does.

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

25 A. No, it didn't.

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

1 one? Any objections to that?
 2 MR. KANTRA: Yeah, that's a fair
 3 question.
 4 THE COURT: I don't think I have
 5 problems with that one. I don't know whether he
 6 can answer it, but --
 7 MR. ALLEN: I don't know -- he can
 8 ask the question --
 9 THE COURT: I'll ask him if he
 10 knows, okay?
 11 MR. SUGGS: I'll ask him.
 12 THE COURT: I've got some concerns
 13 that it's appropriate for him to answer the
 14 question.
 15 MR. ALLEN: No.
 16 MR. FIBICH: They don't want that
 17 asked because they got him -- they tried to get
 18 him to say, you know, you didn't look at our
 19 submission, you didn't look at our submission.
 20 Your Honor, here's the fact. In January of 2007,
 21 when they got the -- the FDA got the information,
 22 they made them change the warning. Their
 23 submission was fraudulent.
 24 THE COURT: And, again, you can ask
 25 that question from other people, but that's 2007.

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

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

1 you to interpret it that way.

2 THE WITNESS: Yeah. It could be
3 that they're exercising less or they're in
4 environments where there's nothing else to do but
5 eat more. They're confined. That's one of the
6 thoughts, in fact, one of the hunches we're
7 playing in a study at Hopkins aimed at improving
8 diet and physical activity in group homes where
9 many individuals with severe mental illness spend
10 their daytimes.

11 THE COURT: And then the last
12 question I'm going to ask you from the jurors is:
13 Did Lilly study -- I think that means the two
14 clamp studies -- address weight gain and its
15 long-term effects?

16 THE WITNESS: Well, no. The clamp
17 studies were designed to be short-term studies of
18 the immediate physiologic effects of the drug, so
19 there was really no way it could study long-term
20 weight gain. The -- I presented the best data
21 that I saw on weight gain, which was from that
22 meta analysis. That was a ten-week -- only a
23 ten-week interval, though.

24 THE COURT: Any followup questions
25 from the attorneys based on those three

1 questions?

2 MR. SUGGS: Not from me,
3 Your Honor.

4 MR. KANTRA: May I have a minute to
5 confer?

6 THE COURT: Please.

7 (Discussion off the record.)

8 MR. KANTRA: No questions.

9 THE COURT: Thank you very much.
10 And I assume that the doctor can be
11 excused.

12 MR. KANTRA: Yes.

13 THE COURT: Thank you very much,
14 Dr. Brancati.

15 Ladies and gentlemen of the jury,
16 that brings us to the end of our trial day.
17 We'll resume tomorrow, same time, and if you
18 could be in the jury room as you were today.
19 Once again, before you leave, I'll remind you,
20 please don't discuss this case with anyone or let
21 anyone discuss it with you. Please try to keep
22 an open mind and not form an opinion until you've
23 heard all of the evidence in this case. Again, I
24 thank you for your service, and I'll see you
25 tomorrow.

1 (Jury out.)

2 THE COURT: Please be seated again.
3 We're outside the presence of the jury. Anything
4 we need to immediately take up before we leave
5 for the day?

6 MR. ALLEN: Aripiprazole is Abilify
7 and ziprasidone is Geodon.

8 THE COURT: Again, give me
9 something to read in the morning and I'll read it
10 to the jury. If you'll give me a pronunciation
11 guide, it might be helpful as well. I just want
12 to make -- Mr. Allen, keeping you from giving
13 what you just said, I wasn't in any ways casting
14 aspersions or doubting your veracity. I just
15 feel I had to give Lilly a chance to agree with
16 you.

17 MR. ALLEN: I can't believe it
18 takes them 24 hours to agree with something like
19 that.

20 THE COURT: I suspect it won't.
21 And, again, if you all -- as I take it, there's
22 nothing critical I have to rule on with
23 deposition testimony or things tomorrow. So if
24 you -- but if you can start giving me what I'm
25 going to need to look at over the weekend. I

1 don't know what I'm doing tonight, but -- and it
2 may be working on other cases. But once you get
3 me the stuff, I can start working on it in the
4 order that you need it.

5 MR. ALLEN: We'll try to get it
6 over here -- something this afternoon,
7 Your Honor.

8 THE COURT: If there's nothing
9 else, then, we'll be in recess and I'll see
10 everybody tomorrow.

11 MR. LEHNER: Thank you, Your Honor.
12 (Trial adjourned at 1:30 p.m.)

1 REPORTER'S CERTIFICATE

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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