Page 1

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

		Page 2		Page 4
1	A-P-P-E-A-R-A-N-C-E-S		1	PROCEEDINGS
2	For the Plaintiff:		2	
3	STATE OF ALASKA		3	THE COURT: We are outside the
4	Department of Law, Civil Division		4	presence of the jury in State of Alaska versus
5	Commercial/Fair Business Section 1031 West 4th Avenue, Suite 200		5	Eli Lilly and Company, 3AN-06-5630. Counsel are
6	Anchorage, Alaska 99501-1994 BY: CLYDE "ED" SNIFFEN, JR.		6	all present.
	Assistant Attorney General		7	There's a pretrial motion. Lilly
7 8	(907) 269-5200 FIBICH, HAMPTON & LEEBRON LLP		8	this morning has filed a motion to exclude
	Five Houston Center		9	certain testimony of presentation material of
9	1401 McKinney, Suite 1800 Houston, Texas 77010		10	Frederick Brancati. I've reviewed that motion
10	BY: TOMMY FIBICH (713) 751-0025		11	and am denying it.
11			12	It's clear to me that I disagree
12	CRUSE, SCOTT, HENDERSON & ALLEN, LLP 2777 Allen Parkway, 7th Floor		13	with Lilly's representation that this has to do
13	Houston, Texas 77019-2133 BY: SCOTT ALLEN		14 15	with the damages phase of this case. It's very clear to me that this is an indication of side
	(713) 650-6600		16	
14	RICHARDSON, PATRICK,		17	effects and consequences of the disease of diabetes that Dr. Brancati will be testifying on
15	WESTBROOK & BRICKMAN		18	that the slides relate to that and are not
16	1037 Chuck Dawley Boulevard, Building A Mount Pleasant, South Carolina 29464		19	case-specific to this case but are more what you
17	BY: DAVID L. SUGGS, Of Counsel (843) 727-6522		20	might call educational materials or examples in
18	(013) 727 0322		21	the general sense of those kinds of things and
19 20			22	that clearly is relevant to the question of the
21 22			23	nature of the disease and the effect that the
23			24	
24 25			25	diabetes was more strongly revealed as a
		Page 3		Page 5
1	A-P-P-E-A-R-A-N-C-E-S, continued		1	consequent, and so I'll deny the motion and on
2			2	that basis.
3 4	For Defendant: PEPPER HAMILTON LLP		3	I've handed both sides my rulings,
Т	301 Carnegie Center, Suite 400		4	
5	Princeton, New Jersey 08543		5	I thought the best way to give you a response to
б	BY: JOHN F. BRENNER GEORGE LEHNER		6	each of the objections was just to use the
0	NINA GUSSACK		7	objections themselves, and write my ruling on the
7	(609) 452-0808	I		
			8	side, that that would make the best record in
8	LANE POWELL, LLC		9	side, that that would make the best record in this case. I make a couple of observations.
	LANE POWELL, LLC 301 West Northern Lights Boulevard		9 10	side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been
8 9	LANE POWELL, LLC		9 10 11	side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been written on the objections as as Roman numeral
	LANE POWELL, LLC 301 West Northern Lights Boulevard Suite 301 Anchorage, Alaska 99503-2648 BY: BREWSTER H. JAMIESON		9 10 11 12	side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been written on the objections as as Roman numeral II, deposition of John Lechleiter was really
9 10	LANE POWELL, LLC 301 West Northern Lights Boulevard Suite 301 Anchorage, Alaska 99503-2648		9 10 11 12 13	side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been written on the objections as as Roman numeral II, deposition of John Lechleiter was really objections to Denise Torres. Was I correct in
9	LANE POWELL, LLC 301 West Northern Lights Boulevard Suite 301 Anchorage, Alaska 99503-2648 BY: BREWSTER H. JAMIESON		9 10 11 12 13 14	side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been written on the objections as as Roman numeral II, deposition of John Lechleiter was really objections to Denise Torres. Was I correct in that? It all seemed to match up.
9 10 11 12 13	LANE POWELL, LLC 301 West Northern Lights Boulevard Suite 301 Anchorage, Alaska 99503-2648 BY: BREWSTER H. JAMIESON		9 10 11 12 13 14 15	side, that that would make the best record in this case. I make a couple of observations. First, I made an assumption that what had been written on the objections as as Roman numeral II, deposition of John Lechleiter was really objections to Denise Torres. Was I correct in that? It all seemed to match up. MR. BRENNER: Yes.
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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 the 4 don't even didn't even come close in this 5 case. 1 opening. 2 MR. ALLEN: Yes, sir. And it is 3 our position. I know you have a jury out and 4 4 don't even didn't even come close in this 5 case. 7 in maccurate risk benefit analysis on this drug 9 an excurate risk benefit analysis on this drug 9 8 to the grave because this ing. 3.5 at least 3.5 9 to 4.5 percent that's in the testimony of the 9 9 objections, primarily because I fiel that a lot 10 of the case related to the off-label promotion, 13 its apparent to me that some of that evidence 13 tis apparent to me that some of that evidence 14 tand begression and indications for which the drug 15 use of Zyprexa was for children and the elderly 14 16 for sustaining a good portion of the objections 19 owns, in fact, not indicated. And so we're sitting 16 10 overy end of the case, and I just wanted to not 24 opportunity. But et me if 1 might, just briefly 25 26 repartion, saving people from frontal 3 lobotomics and electric shock therapy and 16 31 ind the fact which would be assues that would be assues that we the asseed 17 or that door has been opened, you can ask me 2 27		Page 6		Page 8
2that make your objections but make sure3they're real objections, because some of them4don't even didn't even come close in this5case.6The other thing is I guess I'II7just say for the record in reviewing particularly7is uses that Ver excluded from this case. As10of the case related to the off-label promotion11is uses that Ver excluded from this case. As12I've indicated, at least on documentary evidence14can be used for both purposes, but I felt that15may entime to methat some of that evidence16for sustaining a good portion of the objections17that.18may entime a guestion, particularly at the19over yend of the case, and I just warnet to note11million users, the severe disease of1schizophrenia, saving people from frontal3lobotomies and electric shock therapy and its4widespread use.5She's giving a misperception to the6just now going over them, so I haven't had3ubotomies and electric shock therapy and its4biobotomies and electric shock therapy and3biobotomies and electric shock therapy and4biobotomies and electric solok therapy and5THE COURT: And when 11 mean,3again, Tim not pertaps sufficiently attunet4bioplar main and then she told the jury oper3biobotomies and electric solok where were16 <td< td=""><td>1</td><td>not be that, but I would just urge in the future</td><td>1</td><td>opening.</td></td<>	1	not be that, but I would just urge in the future	1	opening.
 3 they're real objections, because some of them 4 don't even - didn't even come close in this 5 case. The other thing is I guess III in the other thing is I guess III objections, primarily because I felt that a lot of the case related to the off-label promotion it is apparent to me that some of that evidence the questions were directly pointed and only the questions were directly pointed and only the questions were directly pointed and only the questions meet directly pointed and only that or multion users, the severe disease of schizophrenia, saving people from frontal biobtomies and electric shock therapy and its that Zyprexa was used for schizophrenia, saving people from frontal biobtomies and electric shock therapy and its that Zyprexa was used for schizophrenia and the she told the jury one that Zyprexa was used for schizophrenia and the she told the jury one that Zyprexa was used for schizophrenia and the she told the jury one there were a lot of stiff is nolicated is and its in dicated is and its is not. there were a lot of stiff is nolicated is and its is not. the defance that his product the world. th			2	
5 case. 5 and we can talk about it further. But it's my 6 The other thing is I guess TII 6 position they've opened the door. They're giving 7 just say for the record in reviewing particularly 6 position they've opened the door. They're giving 7 an inaccurate risk benefit analysis on this drug 7 an inaccurate risk benefit analysis on this drug 8 to the jury because I felt that a lot 10 of the case related to the off-label promotion, and 11 issues that I ve excluded from this case. 40 11 can't emember quite frankly. 12 Ive indicated, at least on documentary evidence, 12 Thirty-five to 45 percent of the 13 if's aparent to me that some of that evidence 13 use of Zyprexa was for children and the elderly 14 and depression and indications for which the drug to 10 was, in fact, not indicated. And so were sitting 16 here talking to the guess. Int Jip is to regular 14 and depression and indications for which the drug to 20 rors rores' dopsition, particularly at the 19 poolet that shouldh't have guest on the drug to 21 that. THE COURT: Well, I guess I'II just 23	3		3	our position. I know you have a jury out and
6 The other thing is 1 guess I'll 6 position they've opened the door. They're 'gring 7 just say for the record in reviewing particularly 8 b 8 Ms. Torres' objections, primarily because I felt that a lot 9 objections, primarily because I felt that a lot 10 of the case related to the off-label promotion 11 is uses a related to the off-label promotion, and 11 is saparent to me that some of that evidence 12 Thirty-five to 45 percent of the 13 is a operation were directly pointed and only 13 use of Cyprexa was for children and the elderly 14 and bepression and indications for which the drug 14 and depression and indication. For which the drug 15 be questions were directly pointed and only 15 world from lobotomics and 23 million users. The 16 here talking to the jury about we're saving the 16 here talking to the jury about we're saving the 17 that was primarily my basis for overruling - or 16 here talking to the jury about we're saving the 16 that was ALLEN: Yes, sir. And 1 - 'I'' 17 world from lobotomics and 24 million users. The 15 million users, the severe disease of sokizophrenia, saving people from f	4	don't even didn't even come close in this	4	maybe we can look I might need to look at this
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 8 Ms. Torres' objections, I sustained a number of 9 objections, primarily because I felt that a lot of the objections are related to the off-label promotion 11 issues that I've excluded from this case. As at it's apparent to me that some of that evidence 13 it's apparent to me that some of that evidence 13 it's apparent to me that some of that evidence 14 it is apparent to me that some of that evidence 17 that was primarily my basis for overruling or 18 for sustaining a good portion of the objections and 1 just wanted to note 21 that. 2 MR. ALLEN: Yes, sir. And I I'm 24 south in the defense yesterday talked about 23 2 million users, the severe disease of 2 schizophrenia, asving people from frontal 3 lobotomies and 2 string a good perform frontal 3 lobotomies and electric shock therapy and its 4 widespread use. 5 She's giving a misperception to the 3 just need for schizophrenia, asving people from frontal 1 is widespread use. 5 State Spiring a misperception to the 3 just need for schizophrenia and the nase toff it heading selling product in the word. 10 So the position that the defense is taking is 1 that Zyerka was used for schizophrenia and the nase sufficiently attuned to prota 1 that Zyerka was used for schizophrenia and 15 the typerawas used for schizophrenia and 15 the typerawas used for schizophrenia and 15 that the defense is taking is 1 that Zyerka was used for schizophrenia and 15 that the defense sufficiently attuned to 17 the to the specifics of some of the things, and those were the one sufficiently attuned to 17 the to the specifics of some of the things, and those were the one sufficiently attuned to 17 the t- to the specifics of some of the things, and hose were the one sufficiently attuned to 17 the to the specifics of some of the things, and hose were the one sufficiently attuned to 17 the to the specifics of some of the things, and hose were the one sufficiently attuned to 17 the to the specifics of some of the things. THE COURT: And thene that s	б	The other thing is I guess I'll	6	position they've opened the door. They're giving
9 objections, primarily because I felt that a lot 9 to 45 percent - that's in the testimony of the 10 of the case related to the off-label promotion 10 witnesses. I think it was Ms. Torres', but I 11 issues that I've excluded from this case. As 11 can't remember quite framkly. 12 Tve indicated, at least on documentary evidence, 13 us of Zyprexa was for children and the elderly 14 can't remember quite framkly. 12 Thirty-five to 45 percent - that's in the testimony of the 13 us opportune to me that some of that evidence 14 and depression and indications for which the drug 15 the questions were directly pointed and only 16 here talking to the jury about we're saving the 17 that. 17 world from lobotomies and 23 million users. The 18 for sustaining a good portion of the objections 9 people that shouldn't have gotten the drug to 20 very end of the case, and I just wanted to note 17 world from lobotomies and 23 million users. The 13 in or the defense systerday talked about 23 22 say this, Mr. Allen. To the extent that 21 million users, the severe disease of 3 or that the door has been opened	7	just say for the record in reviewing particularly	7	an inaccurate risk benefit analysis on this drug
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12 The indicated, at least on documentary evidence, 13 Thirty-five to 45 percent of the 13 it's apparent to me that some of that evidence 14 and depression and indications for which the drug 14 can be used for both purposes, but I felt that 14 and depression and indications for which the drug 15 the questions were directly pointed and only 15 was, in fact, not indicated. And so we're saving the 16 for sustaining a good portion of the objections 16 here talking to the jury about we're saving the 17 world from lobotomies and 23 million users. The 16 fact of the matter is 8 million of those would be 19 on Ms. Torres' deposition, particularly at the 17 world from lobotomies and 23 million users. The 20 that. 21 THE COURT: Well, I guess I'l just 21 and portunity. But Jet me if I might, just briefly 22 say this, Mr. Allen. To the extent that 23 just now going over them, so I haven't had an 23 depositions as being a kind of mixed evidentary 24 widespread use. 3 MR ALLEN: Sevient that 24 3 hobotomies and electric shock therapy and its 4 THE COURT: - outhy the defaces is taking		1		,
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	Page 10		Page 12
1	They clearly opened the door. They stood before	1	But I want to ask one point of
2	this jury yesterday and talked about the risk	2	clarification with respect to the ruling you made
3	benefit analysis, that that's what a doctor does.	3	with Dr. Brancati. We also raised the point that
4	The doctor weighs the living hell of	4	it appears that he is going to make some comments
5	schizophrenia versus the benefits of this drug.	5	about the 2007 label. The report that he filed
6	When they did that, they misled	6	was well before the 2007 label, they never
7	this jury because the risk benefit analysis is a	7	supplemented the report; we've had no opportunity
8	lot different for schizophrenia than it is a lady	8	to cross-examine him about any opinions he may be
9	that's having post-partum depression, a child	9	asked about that. I think there was an explicit
10	that's getting out of his seat too often in the	10	opportunity to supplement reports as I recall.
11	first grade or the elderly who may be stumbling	11	They did not take advantage of that. I'd ask
12	around with dementia. The risk benefit analysis	12	that any testimony that he's going to give on
13	•	13	that be excluded.
14^{13}	does not work with those people.	14	THE COURT: Let me ask Plaintiffs
	The risk benefit analysis works		
15	great with schizophrenia. If you have a truly	15	if he's going to testify about the 2007 label
16	ill person, you have a risk, you can say, okay,	16	or and if so, how do you get that within your
17	we're going to look at the risk of this drug.		report that was provided?
18	When it's someone else, it's a different deal and	18	MR. SUGGS: Your Honor, it's not
19	we're moving the Court that they've opened the	19	really a new opinion. Part of the it comes in
20	door on this issue. We'd like Dr. Gueriguian to	20	connection with his testimony regarding
21	testify. I'm not going to take up any more of	21	comparable rates. He's going to testify that
22	the Court's time. I just would like for you to	22	based upon his review of the scientific
23	be thinking about this, because this will be our		literature, it demonstrates that, in fact, the
24	motion at the conclusion of the day.		incidence of diabetes with Zyprexa is higher than
25	THE COURT: I'm sure I'll be	25	with other drugs and that his opinion on that is
	Page 11		Page 13
	disting the state is here the triangle with some the state	1	
1	thinking about it, but I just will say that if		confirmed by and consistent with the 2003
2	the door has been opened, it's not readily		ConSensus statement, and further, by the recent
3	apparent to me, at least at this point. If the	3	label change
4	door is opened, we'll take that up, but right now	4	THE COURT: Was he deposed?
5	risk benefit analysis in a general sense is still	5	MR. SUGGS: Pardon?
6	in a general sense and I haven't heard specific	6	THE COURT: Was he deposed?
7	differences of risk benefit analysis coming out	7	MR. SUGGS: He was deposed in
8	or any of those kinds of things nor have I heard	8	January of 2007, Your Honor. April of 2007.
9	the statistics or any of that kind of thing.	9	THE COURT: So before the 2007
10	I don't have that evidence	10	label.
11	competently put in front of us at this point, and	11	MR. SUGGS: Yes, he was deposed
12	so I'll just tell you that maybe after today's	12	before the 2007 label.
13	testimony I'll think the door's been open, but	13	THE COURT: And was there some
14	based on based on the opening, the door may be	14	additional disclosure?
15	open to the bipolar mania issue that was	15	MR. SUGGS: There was no additional
16	discussed and there was a little bit of colloquy	16	disclosure, sir.
17	between counsel as to whether it was approved or	17	THE COURT: I'm going to let him
18	whether it wasn't approved. But right now,	18	testify as to comparable rates in 2003, but the
19	that's all I see the door being open.	19	2007 stuff needs to not be gone into.
20	MR. FIBICH: We would like the	20	MR. SUGGS: Your Honor, if, in
21	opportunity to talk to the Court about that at	21	fact, they cross-examine him about comparable
22		22	rates, would we not be able to haven't they
22	the conclusion of today's testimony.	22	
23	MR. LEHNER: Your Honor, we'd be	23	then opened the door
	MR. LEHNER: Your Honor, we'd be		then opened the door
23	• •	23	

	Page 14		Page 16
1	whether or not I feel the door has been opened	1	want people surprised. This is a very close
2	and questions may be asked that will elicit that	2	question to me as to whether or not there's any
3	response, and if I think it's a fair response	3	surprise going on.
4	we'll be able take that up, too.	4	MR. FIBICH: How can they be
5	MR. SUGGS: Very well, Your Honor.	5	surprised about their label? The fact of the
6	THE COURT: But I'm not going to	6	matter is
7	preclude what the doors open. All I'm going to	7	THE COURT: That's not what the
8	say is for the time being if he didn't in his	8	surprise is. The surprise is whether or not this
9	report discuss 2007, and there was no	9	witness was going to offer an opinion or offer
10	supplementation to indicate that, I'm not going	10	testimony about the 2007 label and what it means
11	to let him refer to matters that weren't fairly	11	for this case. That's the question that I'm
12	disclosed in his report or supplemented or gone	12	thinking about.
13	into in deposition.	13	MR. LEHNER: Well, we'll be careful
14	MR. SUGGS: Very well, Your Honor.		in our questioning, Your Honor.
15	And if I think the door has been opened, I'll ask	15	THE COURT: You guys the
16	to approach the bench so we can discuss it?	16	Plaintiffs can renew this after we hear
17	THE COURT: That would be the best	17	cross-examination and I'll I'm going to think
18	way to handle it, yes.	18	about this one more. It's a very close question
19	MR. SUGGS: Okay. Thank you.	19	in my mind as to notice. Right now, I'm going to
20	MR. LEHNER: And I have just one	20	leave it the way that it is, but by the end of
21	question just so I have a sense of sort of	21	the day I'm not sure what I'll do.
22	where the door may begin to swing at what point.	22	MR. SUGGS: Thank you, Your Honor.
23	I'm assuming he can be cross-examined on	23	THE COURT: Any other pretrial?
24	comparable rates since that's within his report	24	MR. LEHNER: I'm sorry I'm sorry
25	but if there's some questioning about well, in	25	to take up time, Your Honor. The only other
	Page 15		Page 17
1	light of the 2007 label, how can you maintain	1	question is as we've tried to put these
2	light of the 2007 label, how can you maintain this opinion about comparable rates, I would see	2	question is as we've tried to put these deposition pieces together, we did file this
2 3	light of the 2007 label, how can you maintain this opinion about comparable rates, I would see that swinging the door wide open	2 3	question is as we've tried to put these deposition pieces together, we did file this motion about the sort of word salad that's kind
2 3 4	light of the 2007 label, how can you maintain this opinion about comparable rates, I would see that swinging the door wide open THE COURT: I'm not sure. You 're	2 3 4	question is as we've tried to put these deposition pieces together, we did file this motion about the sort of word salad that's kind of going to be created if we can't try to line
2 3 4 5	light of the 2007 label, how can you maintain this opinion about comparable rates, I would see that swinging the door wide open THE COURT: I'm not sure. You 're going to have to fashion your questions	2 3 4 5	question is as we've tried to put these deposition pieces together, we did file this motion about the sort of word salad that's kind of going to be created if we can't try to line these up. We'd be happy to show you a little
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	Page 18		Page 20
1	might really be misleading as to what the witness	1	MR. ALLEN: We will
2	is saying in the overall context of the	2	THE COURT: It will make the
3	deposition.	3	deposition a little bit longer, but it gives
4	I will consider applications to	4	the I want this to be understandable to the
5	have particular snippets of what the defense	5	jury and I'm trying to be fair to both of you,
6	wants based on reviewing the entire deposition	6	obviously, and so that's how I'm going to look at
7	included in the Plaintiff's presentation of that	7	it.
8	testimony, but that's going to be the only limit.	8	I guess what I'll say is I'm going
9	The one thing that I'm really concerned about is		to if I what I'm very concerned about is
10	because I've seen it many times, is the	10	the idea of taking what some very precise
11	Plaintiffs designate a very specific, precise	11	testimony that would be might be taken and
12	series of questions that they want to do, and	12	used in an examination of one side and kind of
13	then the Defendant designates the entire	13	using the fact that it's a deposition to bury the
14	deposition to hide it all, to bury it all and I'm		whole thing, and that I don't like at all.
15	not going to allow that.	15	MR. LEHNER: I don't think that's
16	The general rule is going to be is	16	what we're trying to do. And if somebody on your
17	that they can present their deposition testimony	17	side can whoever's going to be on your side.
18	and then when it's your turn, you can present	18	Is that going to be you?
19	your deposition testimony. And that's how we're	19	MR. ALLEN: Let me say that's
20	going to proceed, but to the extent I think that	20	exactly what they're trying to do. Anyway, we
21	doing that will lead to a misleading of the jury	21	have your ruling, and we'll abide by it.
22	or I really think it's a completeness issue so	22	THE COURT: And is that, Mr. Allen,
23	that which is really a question of getting the	23	the process that has been described, is that
24	jury a fair picture of what this witness said,	24	acceptable to you that you'll get with whom?
	that's what I believe completeness is about, I	25	MR. LEHNER: And if we're going to
25	*	25	· ·
-	Page 19	_	Page 21
1	will consider individual applications on that		start playing depositions, we need to get people
2	basis.	2	working on this right away.
3	But as to the general rule will	3	THE COURT: Right. That actually
4	be the rule that was discussed previously that	4	brings up one more thing. I took care of the two
	we're going to do this in a staggered fashion	5	you gave me. Tell me who is next.
	just as would happen if the witness were a live	6	63
7	witness.	7	THE COURT: Tell me and let me know
8	MR. LEHNER: Could I suggest a	8	when, probably you need it by. I hope I have the
9	process then, Your Honor, to make to see if we	9	weekend.
10	can accommodate that we would designate somebody	10	MR. ALLEN: You'll have some more
11	and the Plaintiffs will designate somebody and	11	on your desk hopefully this afternoon. As a
12	they're probably going to have to sit down	12	matter of fact, I'll get that done.
13	probably as we speak and try to reconcile these	13	THE COURT: Are they again, let
14	and then just bring to you the parts where we may	14	me know when you're hoping to play these people
15	disagree.	15	so I have my deadline.
16	THE COURT: I recognize that that's	16	MR. ALLEN: Yes, sir. I'll do
17	the implications of my ruling and, yes, that	17	that.
18	seems to be the best process. The other thing I	18	MR. LEHNER: And we'll look at our
19	guess I'll certainly indicate is that to the	19	objections with your comments in mind.
20	extent that the Defendants need to replay a few	20	THE COURT: Okay.
21	portions of what the Plaintiffs have already	21	We'll then bring the jury back in,
22	played to give them the context in their	22	I'll read them some introductory instructions and
23	deposition testimony presentation, I'll allow	23	we'll take it from there. We'll be off record.
24	that as well.	24 25	(Break.) THE COURT: Please be seated. We
25	MR. LEHNER: Thank you.		

	Page 22		Page 24
1	are back on the record. All members of the jury	1	Five, how reasonable was the
2	are present. Good morning, ladies and gentlemen	2	witness' testimony considered in light of all the
3	of the jury. Thank you for being here so	3	evidence in the case?
4	promptly, and I appreciate your putting up with	4	Six, was the witness' testimony
5	the patience for the security door. We sometimes	5	contradicted by what that witness has said or
6	have problems because we mess up in our chambers.	6	done at another time or by the testimony of our
7	Sometimes it's because you're still learning the	7	witnesses or by other evidence.
8	process and sometimes it's because that door just	8	If you believe that a witness
9	is a pain in the neck.	9	testified falsely as to part of his or her
10	And I appreciate you putting up	10	testimony, you may choose to distrust other parts
11	with us. If somebody gets trapped between the	11	also, but you are not required to do so. You
12	doors, we will rescue you, I assure you.	12	should bear in mind that inconsistencies and
13	But I thank you for your patience	13	contradictions in a witness' testimony or between
14	and we'll try to make sure it works as best as we	14	his or her testimony and that of others do not
15	can make it work.	15	necessarily mean that you should disbelieve the
16	Let me give you some instructions	16	witness. It is not unusual for persons to forget
17	before we begin the presentation of the evidence	17	or to be mistaken about what they remember and
18	in this matter.	18	this may explain some inconsistencies and
19	The opening statements are complete	19	contradictions.
20	and I have explained to you some of the law you	20	It is also common for two honest
21	should keep in mind as the trial moves forward.	21	people to witness the same event and see or hear
22	The presentation of evidence is about to begin	22	things differently. It may be helpful when you
23	now.	23	evaluate inconsistencies and contradictions to
24	I have already told you that your	24	consider whether they relate to important or
25	job is to evaluate the evidence, although I will	25	unimportant facts. You may believe all, part or
	Page 23		Page 25
1	be giving you detailed instructions after the	1	Page 25 none of the testimony of any witness. You need
1 2		1 2	none of the testimony of any witness. You need not believe a witness even though his or her
	be giving you detailed instructions after the presentation, I also want to give you instruction which may help you deal with evidence as it is	1 2 3	none of the testimony of any witness. You need not believe a witness even though his or her testimony is uncontradicted. But you should act
2 3 4	be giving you detailed instructions after the presentation, I also want to give you instruction which may help you deal with evidence as it is offered. I will give you those instructions now.	2 3 4	none of the testimony of any witness. You need not believe a witness even though his or her testimony is uncontradicted. But you should act reasonably in deciding whether or not you believe
2 3 4 5	be giving you detailed instructions after the presentation, I also want to give you instruction which may help you deal with evidence as it is offered. I will give you those instructions now. Every person who testifies under	2 3 4 5	none of the testimony of any witness. You need not believe a witness even though his or her testimony is uncontradicted. But you should act reasonably in deciding whether or not you believe a witness or how much importance to attach to
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	Page 26		Page 28
1	the testimony of an expert witness. You need not	1	rulings, as these matters will be determined by
2	believe an expert witness even if the testimony	2	the law and will not reflect anything about the
3	is uncontradicted but you should act reasonably	3	merits of the case or my views of the evidence of
4	in deciding whether or you believe an expert and	4	the witnesses.
5	how much importance to attach to the expert's	5	My rulings that exclude evidence or
6	testimony.	6	bar questions are designed to help you decide the
7	You may have exhibits such as		case fairly. Of course, if certain evidence is
8	documents, pictures or objects to consider as	8	excluded, you must disregard it. You may not
9	evidence. When deciding how much to rely on an	9	speculate about why the evidence was excluded or
10	exhibit in reaching a verdict, you should examine	10	what it may have been.
11	its contents and consider how it relates to the	11	Upon allowing testimony or other
12	other evidence in the case. Keep in mind that	12	evidence to be introduced over the objection of
13	exhibits are not necessarily better evidence than	13	an attorney, I am not implying any opinion as to
14	testimony from witnesses.	14	the importance of the evidence. As stated
15	It is possible that I will ask	15	before, you are the exclusive judges of the
16	questions of witnesses called by the parties. If	16	
17	• • •	17	credibility of all witnesses and of the
18	I do so, you should consider the resulting	18	importance and the effect of all evidence. When I sustain or grant an
19	testimony as you would any other testimony in this case. You should not assume that because I	19	objection to a question, you must disregard the
20		20	
20	ask questions, I have an opinion about the case.	20	question entirely. You may not draw any
21	It is your job and yours alone to evaluate the evidence and to decide what witnesses to believe	21	inference from the wording of it or speculate as
			to what the witness would have said if permitted
23 24	and what weight to give to testimony.	23 24	to answer the question.
24 25	There are rules of law that present	24	I have just described the ways that
25	some types of information from being presented as	25	evidence may be presented. Regardless of the way
-	Page 27		Page 29
1	evidence in a court of law. That is why		it is presented, evidence is either direct or
2	objections may be made to certain questions of	2	circumstantial. Direct evidence, if you accept
	councel enguare of witnesses or exhibite. There	2	
3	counsel, answers of witnesses or exhibits. There	3	it as true, proves a fact. Circumstantial
4	will likely be conferences and legal arguments	4	it as true, proves a fact. Circumstantial evidence, if you accept it as true, proves a fact
4 5	will likely be conferences and legal arguments outside of your presence. I know that you will	4 5	it as true, proves a fact. Circumstantial evidence, if you accept it as true, proves a fact from which you may infer that another fact is
4 5	will likely be conferences and legal arguments outside of your presence. I know that you will wonder what is being discussed and after such	4 5 6	it as true, proves a fact. Circumstantial evidence, if you accept it as true, proves a fact from which you may infer that another fact is also true. Let me give you a common example:
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4 5 7 8 9 10	will likely be conferences and legal arguments outside of your presence. I know that you will wonder what is being discussed and after such discussions, why some evidence must be excluded. These matters are governed by the rules of evidence and the rules of the court. Basically, these rules are designed	4 5 7 8 9 10	it as true, proves a fact. Circumstantial evidence, if you accept it as true, proves a fact from which you may infer that another fact is also true. Let me give you a common example: Let us pretend that as a juror you are asked to decide the following question: Did snow fall during a particular night? Direct evidence would be a witness
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	Page 30		Page 32
1	Some jurors prefer to take notes as evidence is	1	about a question if it is necessary to provide a
2	presented; other jurors prefer not to do so.	2	further instruction about the topic. But if I do
3	Each juror may decide whether or not to take	3	not ask a question you submitted, please
4	notes. It is not necessary for you to take	4	understand that you are not to draw any inference
5	notes, but it is necessary that you carefully	5	whatsoever from my decision not to ask that
6	consider all the evidence in the case. Do not	6	question.
7	let note-taking interfere with your consideration	7	As I have explained to you about
8	of the evidence. Your primary function is to see	8	questions asked by attorneys, we have evidence
9	and hear the witnesses and observe other and	9	rules that dictate what can and cannot be asked.
10	observe other evidence.	10	I will treat your questions in the same manner as
11	Each time that you are excused from	11	those of the attorneys, and you should treat my
12	the courtroom, your notepads must be placed on	12	rulings on questions submitted by the jury as you
13	your chairs face down. When you begin	13	do my rulings on questions asked by the
14	deliberations, you will have your notes with you.	14	attorneys. Each juror must decide independently
15	But please remember, a juror's notes are not	15	whether or not to ask questions of any witnesses.
16	necessarily more accurate than the memory of	16	You should not discuss whether to ask questions
17	another juror who chose to carefully consider the	17	among yourselves. You should not give answers to
18	evidence without taking notes. When the case is	18	jurors' questions a disproportionate weight
19	over, your notes will be collected and destroyed.	19	merely because a juror asked the question.
20	Our Alaska trial procedure assumes	20	Finally, please keep in mind that
21	that generally the parties will call the	21	the purpose of allowing you to submit the
22	witnesses and question them. As I have told you,	22	requests is to help you understand the evidence.
23	it is possible that I may ask some additional	23	You should only ask questions that will help you
24	questions to fill out a witness' testimony.	24 25	clarify what you have heard, rather than
25	Occasionally you may be confused about what a	25	exploring some theory or argument you might have
	Page 31		Page 33
1	witness meant to say or you may think that a	1	concerning the testimony. If you decide to ask
2	witness has omitted something important by	2	questions, you should not allow yourselves to
3	mistake. In most cases these matters will be	3	become aligned with any party or attempt to help
4	clarified before the witness completes his or her	4	or respond to any party with your questions. You
5	testimony. If not, you too may ask questions of	5	must remain neutral and impartial throughout this
6 7	the witnesses.	67	trial and not assume the role of investigator or
-	Here is what you may do. After a	8	advocate.
8 9	witness has been fully examined by both sides, you should write down a short description of your	9	As I told you, this case will probably take about four weeks to conclude. From
10	confusion or the matter that you think was	10	now until the end of the trial when you go to the
11	inadvertently omitted on the pad that you have	11	jury room to decide this case, you may not
12	and pass your note to the in-court clerk. As	12	discuss this case with or offer any opinion about
13	with any question asked by an attorney, I will	13	it to anyone else. This means not with anyone
14	review the questions you submit to determine if	14	else on the jury and also not with any other
15	they comport with the rules of evidence and the	15	person, including court personnel. You are
16	law of this case. I will also go over the note	16	expected to evaluate the evidence independently
17	with the parties.	17	until you are told to deliberate as a group.
18	I may decide that additional	18	As the case moves along, you should
19	questions should be asked by the parties or by	19	keep in mind that evidence can only be presented
20	me, or I may decide that the witness has	20	a piece at a time. It is common for people, as
21	testified as well as he or she can or as fully as	21	they hear parts of a story and as they try to
22	permitted by law and no further questions will be	22	make sense of it, to draw certain conclusions
I	asked. If I determine that a question is not	23	about the actors or about the events which go
23	asked. If I determine that a question is not		
23 24 25	appropriate or relevant, I may or may not tell you what the question is. I will only tell you	24 25	beyond anything they have actually heard. This 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 a laready formed. 6 Under our system, the Plaintiff 7 patts on their evidence. 8 on their evidence. 9 you should work to keep an open mind until 9 sides, you should work to keep an open mind until 9 you have heard all of the evidence. 11 Until the trial is over, you must 12 avoid any contact with may of the persons whoar 13 participating in the trial. This includes the 14 partice, the lawyers, the witnesses, and any 15 persons whon you see in close contact with these 16 individuals. Do not ceal newspaper articles 10 bo not read newspaper articles 11 hee vidence, research any investigations 12 THE CLRK: For the record, sir, 13 matters that you are to decide the case only on 14 penthem during the trial you cannot see or	1			
2 you have heard all of the evidence as it may 2 matters that come up that must be heard outside 3 cause you to resist giving fair consideration to other evidence which is inconsideration to 4 other evidence which is inconsideration to other evidence which is inconsideration 5 conclusions you have already formed. and interruptions, and 1 want to assure you they 7 puts on its evidence and then the Defendant puts and interruptions, and 1 want to assure you they 9 sides, you should work to keep an open mind until 9 Is the State ready to present its 10 you have heard all of the evidence. 10 first witness? 11 Until the trial is over, you must 11 first witness? 12 participating in the trial is over, you must 13 MR. SUGGS? We are, Your Honor. 12 avaid any contact with thay of the persons who are 13 MR. SUGGS? Word Honor, Iadies and 14 participation to trial or econd case only on 14 gentleme of the jury, the State of Alaska calls 15 persons whom you see in close contact with these 15 Dr. Fred Brancati as an expert witness. 16 mHE COURT: And sir, if you could 17 remain stand		resist the temptation to draw conclusions before	1	interruption before trial, there inevitably are
3 cause you to resist giving fair consideration to 4 of your presence. The purpose of having these 4 other evidence which is inconsistent with 4 hearings without the jury is to ensure a fair 5 conclusions you have already formed. 5 thearings without the jury is to ensure a fair 6 Under our system, the Plaintiff 5 that. I. Tapologize in advance for these delays 7 puts on its evidence and then the Defendant puts 5 and interruptions, and I want to assure you they 9 sides, you should work to keep an open mind until 10 is the State ready to present its 10 you have heard all of the evidence. 10 first witness? 11 Until the trial is over, you must 11 MR. SUGGS: We are, Your Honor. 12 avoid any contact with any of the persons whoan is enderson that such and persons whoan you see in close contact with these 16 individuals. Do not conduct any investigations, 17 mermis standing behind the witness? 18 Remember that you are to decide the case only on the vidences research and puts about this case ont 18 put you under oath. 12 Do not read howspaper articles 17 mermis standing behind the witness? 17<			2	
4other evidence which is inconsistent with 54hearings without he jury is to ensure a fair 55conclusions you have already formed. 6Under our system, the Plaintiff 7trial. I apologize in advance for these delays 66under our system, the Plaintiff 9sides, you should work to keep an open mind until 10you have heard all of the evidence.11Until the trial is over, you must 13and you have heard all of the evidence.1012avoid any contact with any of the persons who are 13marking in the trial. This includes the 131114parties, the lawyers, the witnesses, and any 15persons whom you see in close contact with these 161616individuals. Do not conduct any investigations, 17visit the site of events or research any issue.16THE COURT: And sir, if you could 1719the evidence presented here in court.19FREDERICK BRANCATI, 191820Do not read newspaper articles 21about the case or watch or lists en to television 22121223atrial is over. Do not read about this case or 24any matters related to this case on the Internet.24and and I will correct the situation.10Free-d-er-i-ck.3If you have a physicid or other 411Brancati. Last name is B as in boy.4the clerk or by raising your hand, a note to the clerk or by raising your hand, 410115the arts nown goo and pholem that you watch a note to the clerk or by raising your hand, 411 </td <td></td> <td>5</td> <td>3</td> <td>1</td>		5	3	1
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6 Under our system, the Plaintiff 6 and interruptions, and I want to assure you they 7 puts on its evidence. In order to be fair to all 9 occur only to discuss important matters when 9 sides, you should work to keep an open mind until 9 Is the State ready to present its 10 you have heard all of the evidence. 10 first wirness? 11 Until the trial is over, you must 11 MR. SUGGS: Your Honor. 12 avoid any contact with any of the persons who are 13 MR. SUGGS: Your Honor. 12 participating in the trial. This includes the 13 MR. SUGGS: Your Honor. 13 participating in the trial. This includes the 15 Dr. Fred Brancatia an expert witness. 16 individuals. Do not conduct any investigations, 16 THE COURT: And sir, if you could 17 visit the site of events or research any issue. 18 18 18 19 12 about the case on watch or listen to television 19 FREDERICK BRANCATI, 20 Thear a witness or an attorney, please raise your 19 12 18 12 21 thair so with or sis are or your important work, Do not hesitac </td <td></td> <td></td> <td></td> <td></td>				
7 puts on its evidence and then the Defendant puts 8 on their evidence. 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 particis, the lawyers, the witnesses, and any 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 con 19 the evidence presented here in court. 20 Do not read newspaper articles 21 about the case or watch or listen to television 21 at any time during the trial you cannot see or 23 trial is over. Do not read about this case or 24 any matters related to this case on the Internet. 25 T at any time during the trial you cannot see or 24 and and I will correct the situation. 25 T hear a witness or an attorney, please traise your 26<				
 a on their evidence. In order to be fair to all 9 sides, you should work to keep an open mind until 9 sides, you should work to keep an open mind until 19 sides, you should work to keep an open mind until 10 the relation of the evidence. 11 Until the trial is over, you must 12 avoid any contact with the trial. This includes the 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 12 alobut the case or watch or listen to television. 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. 23 If you have a physical or other 44 problem that you would like to bring to my 5 attention, or if you feel ill or need to go to 64 the rest room, please let me know by sending a 7 note to the clerk or by raising your hand, and 21 ladies and gentemen of the jury, smoettimes 111 outside Baltimore, Maryland. 24 any fue during that 1 need to give you a note about. 25 THE WITNESS: My name is Frederick, 3 F-re-d-e-r-i-c-k. 37 The Courrest the situation. 48 the clerk will deliver the note to me. 9 I want you to be comfortable as you 19 Exerce EXAMINATION 64 the rest or 0 the situe to 10 or more of any problem that you have. And, and 36 the clerk will deliver the note to me. 9 I want you in advause that 10 to inform me of any problem that you have. And, 41 the during that 1 need to give you a note about. 37 orbet the clerk or by raising your hand, and 2 wor focused on the lavy no be somfortable as you 38 netheming like		•	7	
 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. 10 Do not read newspaper articles 12 or radio news stories about this case until the 21 about the case or watch or listen to television 21 or bon orews stories 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 25 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, 15 Mr. Borneman usually sees you and he lets me know 16 curry our your important work. Do not hexitat 16 but if we don't see you raising your hand, 17 say, Judge, I have a question. Judge, I've got 18 something that I need to give you a note about. 19 you've got your hand raised, please feel free to 17 say, Judge, I have a question. Judge, I've got 18 something that I need to give you a note about. 19 you've got your hand raised, please feel free to 10 you've got your hand raised, please feel free to 11 interrupt and let us know that. 22 Now than 23 you've got your hand raised, please feel free to 24 jonns Hoykins University. 24 must wam you in advance that 25 mething like that. 26 proce. 27 A. I'm a physician and a faculty member at 29 johns Hoykins University. 			8	
 10 you have heard all of the evidence. 11 Until the trial is over, you must a void any contact with any of the persons who are 11 m. SUGGS: Your Honor, Iadies and 12 persons whom you see in close contact with these 13 m. SUGGS: Your Honor, Iadies 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 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 or 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 26 Page 37 1 hear a witness or an attorney, please rate you? 27 hand and I will correct the situation. 31 If you have a physical or other 42 problem that you would like to bring to my 51 attention, or if you feel ill or need to go to 61 the clerk will deliver the note to me. 9 9 9 9 9				•
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		•		· ·
	23	there may be delays and interruptions in the	23	
24 trial. Although every effort has been made to24 expert witness to testify about diabetes and			24	
25 deal with matters that may cause a delay or 25 whether or not the use of Zyprexa increases the		deal with matters that may cause a delay or	25	whether or not the use of Zyprexa increases the

	Page 38		Page 40
1 risk	c of diabetes?	1	Q. And you graduated magna cum laude,
	A. They have.	2	correct?
	2. And has the State also retained you to	3	A. Correct.
· ·	tify about whether Zyprexa causes more	4	Q. And then you went to medical school
	betes than other antipsychotic drugs?	5	after that?
	They have.	6	A. Medical school at Columbia University in
	Okay. And have you prepared a report		New York City.
	arding your opinions on those issues and the	8	Q. And what year did you graduate from
		9	medical school?
	sis for your opinions?	10	A. Graduated in 1985.
		11	
	And I don't believe you have that report		Q. And did you then take an internship and
	h you, do you, sir?		residency?
	A. No, I don't.	13	A. Yes, I did, at the University of
14 15 D	MR. SUGGS: Your Honor,		Pittsburgh.
	Brancati's report is Plaintiff's Exhibit	15	Q. In what field?
	127. I'm not going to be offering it into	16	A. That was in internal medicine.
	dence, but counsel have a prior agreement that	17	Q. And what is meant by the phrase
	ir respective expert witnesses may have their	18	"internal medicine"?
	orts with them when they testify for	19	A. Internal medicine is the training ground
	erence, if necessary.	20	for physicians who practice diagnosis and
21	THE COURT: And that is true?		treatment of conditions in in adults. Many
22	MR. LEHNER: Yes.		trainees go on to careers in organ-oriented
23	THE COURT: And that's the rule		specialties like cardiology and pulmonary
	'll follow.		medicine. I stayed in general internal medicine.
25	MR. SUGGS: Very well, Your Honor.	25	Q. And you were in that residency program
	Page 39		Page 41
1 Q	(BY MR. SUGGS) Dr. Brancati, before we	1	from 1985 through 1989; is that correct?
2 talk	about your opinions about Zyprexa, I'd first	2	A. Yes, three years of residency and then a
	e to ask you some questions about your	3	year as a chief resident.
	kground, your training and experience in the	1	
	d of diabetes.	4	•
<i>c</i>	lu of diabetes.	4 5	Q. What were your responsibilities as chief resident?
6	First off, sir, how old are you?		Q. What were your responsibilities as chief
		5	Q. What were your responsibilities as chief resident?A. The chief resident is one of the leaders
	First off, sir, how old are you?	5	Q. What were your responsibilities as chief resident?A. The chief resident is one of the leaders of the residency program, making schedules,
7 A	First off, sir, how old are you? A. I'm 48. D. You're married?	5	Q. What were your responsibilities as chief resident?A. The chief resident is one of the leaders
7 A 8 Q	First off, sir, how old are you? A. I'm 48. J. You're married? A. I'm married.	5 6 7 8	Q. What were your responsibilities as chief resident?A. The chief resident is one of the leaders of the residency program, making schedules, teaching, organizing the practice of the
7 A 8 Q 9 A 10 Q	First off, sir, how old are you? A. I'm 48. J. You're married? A. I'm married.	5 6 7 8 9	 Q. What were your responsibilities as chief resident? A. The chief resident is one of the leaders of the residency program, making schedules, teaching, organizing the practice of the trainees. Q. And after you completed your residency,
7 A 8 Q 9 A 10 Q 11 cor	 First off, sir, how old are you? A. I'm 48. A. You're married? A. I'm married. B. Your wife is a doctor also. Is that 	5 6 7 8 9 10	Q. What were your responsibilities as chief resident?A. The chief resident is one of the leaders of the residency program, making schedules, teaching, organizing the practice of the trainees.
7 A 8 Q 9 A 10 Q 11 cor	 First off, sir, how old are you? A. I'm 48. D. You're married? A. I'm married. D. Your wife is a doctor also. Is that rect? A. Yes, also at Hopkins. 	5 6 7 8 9 10 11 12	 Q. What were your responsibilities as chief resident? A. The chief resident is one of the leaders of the residency program, making schedules, teaching, organizing the practice of the trainees. Q. And after you completed your residency, did you then go on to get a post-doctoral fellowship in internal medicine at Johns Hopkins
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	Page 42		Page 44
1	programs take special fellowships to train as	1	related to the trials that I'm involved in. And
2	cardiologists or pulmonary specialists,	2	then the rest of the time is spent on research
3	endocrinologists. Relatively few go into	3	and on mentorship of students and junior faculty
4	research-oriented fellowships in general internal	4	and trainees who are interested in research in
5	medicine prevention, epidemiology.	5	diabetes and obesity.
6	Q. You went into the research side of it?	6	Q. And how many people do you spend how
7	A. Yes.	7	many people do you mentor in their research?
8	Q. Did you also obtain a master's degree in	8	A. It it's a lot. I'm indirectly
9	epidemiology?	9	responsible for all 70 faculty in the division,
10	A. That is correct.	10	but in my own area of diabetes and obesity it's
11	Q. What is epidemiology?	11	about seven faculty and about an equal number of
12	A. Epidemiology is the study of patterns of	12	post-doctoral fellows and students.
13		13	Q. What is the focus of your research?
14	disease in populations with an aim to identify	14	
	causes of disease as a means to develop		A. My expertise is in diabetes epidemiology
15	strategies for prevention. It started in the	15	with an eye towards prevention, so I do
16	field of infectious diseases and that's where the	16	large-scale studies trying to identify risk
17	term epidemics come from. But in the past 30 or		factors for diabetes, studying the consequences
18	40 years scientists have taken the methods		of diabetes, both established consequences and
19	they've learned from the study of infectious	19	maybe new consequences, and then I conduct
20	disease and figured out how to apply it to	20	clinical trials either aimed at preventing
21	chronic diseases like heart disease, obesity or	21	diabetes or preventing its long-term
22	diabetes.	22	complications.
23	Q. After completing that, am I correct that	23	Q. Okay. And we're paying you a fee for
24	you joined the faculty of John Hopkins	24	your the time that you spend as an expert in
25	University?	25	connection with this case, correct?
	Page 43		Page 45
1	A. Yes, 1992.	1	A. Yes.
2	Q. Is the John Hopkins University	2	Q. Okay. And where does that fee go?
3	epidemiology program well-known around the world?	3	A. I donate the fee to the university to
4	A. Yeah. It's one of the biggest and	4	support the the research mission related to
5	oldest departments around.	5	diabetes and obesity, so
6	Q. And you're presently a full professor of	6	Q. Do you receive any personal benefit at
	medicine and epidemiology at John Hopkins and		all for the fee that we're paying for your
, 8	also director of the Division of General Internal		
9	Medicine; is that correct?	8	services? A. I don't take a lot of money myself, but
10			
11	A. That's correct. The they'll be mad at me back in Baltimore if I don't make you put	10 11	I get a lot of satisfaction out of supporting the diabetes research effort.
12	the S on the end of Johns.	12	
13			
	Q. Sorry.	13	scientific journal?
14	A. That's okay.	14	A. Peers in science, we use the term
15	Q. Could you tell the jury what percentage of your time you spend teaching, doing research,	15	"peer" to mean other researchers at other
16	or your time you spend teaching, doing research.	16	universities who are in a position to review our
17		1	
	doing administrative matters and so forth?	17	work, either our grant applications or our papers
18	doing administrative matters and so forth?A. Sure. About four years ago I took a	18	in an impartial way and give, you know, candid,
18 19	doing administrative matters and so forth?A. Sure. About four years ago I took adivision director job. So now about 25 percent	18 19	in an impartial way and give, you know, candid, anonymous opinion about the quality of the
18 19 20	doing administrative matters and so forth?A. Sure. About four years ago I took adivision director job. So now about 25 percentof my time is spent doing administrative work for	18 19 20	in an impartial way and give, you know, candid, anonymous opinion about the quality of the science.
18 19 20 21	doing administrative matters and so forth? A. Sure. About four years ago I took a division director job. So now about 25 percent of my time is spent doing administrative work for a group of 70 faculty and trainees and students	18 19 20 21	in an impartial way and give, you know, candid, anonymous opinion about the quality of the science. So for us the gold standard what
18 19 20 21 22	doing administrative matters and so forth? A. Sure. About four years ago I took a division director job. So now about 25 percent of my time is spent doing administrative work for a group of 70 faculty and trainees and students to go along with them. So that's about 25	18 19 20 21 22	in an impartial way and give, you know, candid, anonymous opinion about the quality of the science. So for us the gold standard what I train young people there to do is write
18 19 20 21 22 23	doing administrative matters and so forth? A. Sure. About four years ago I took a division director job. So now about 25 percent of my time is spent doing administrative work for a group of 70 faculty and trainees and students to go along with them. So that's about 25 percent of my time. About 5 or 10 percent of my	18 19 20 21 22 23	in an impartial way and give, you know, candid, anonymous opinion about the quality of the science. So for us the gold standard what I train young people there to do is write excellent papers, submit it for review to
18 19 20 21 22	doing administrative matters and so forth? A. Sure. About four years ago I took a division director job. So now about 25 percent of my time is spent doing administrative work for a group of 70 faculty and trainees and students to go along with them. So that's about 25	18 19 20 21 22	in an impartial way and give, you know, candid, anonymous opinion about the quality of the science. So for us the gold standard what I train young people there to do is write

	Page 46		Page 48
1	anonymously to peer reviewers who look at the	1	you've been a member of national advisory
2	science, look at the paper, and then make a	2	committees?
3	determination as to whether or not it's valid	3	A. Yeah, many.
4	enough to be acceptable for publication and	4	Q. Did they have to do with diabetes as
5	dissemination.	5	well?
6	Q. And why are the reviews anonymous?	6	A. Yes.
7	A. If they weren't anonymous, the reviews		Q. Have you been a consultant for any drug
8	could be quite political. I have a friend	8	companies regarding diabetes epidemiology?
9		9	A. Yes, I have.
10	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	11	A. Most recently Pfizer and Novartis.
12	there. There would be a lot of there would be	12	Q. Okay. Let's talk generally about what
13	a lot of favor exchanged, a lot of people who	13	diabetes is, how it develops and what the
14	are concerned about recriminations. This way	14	complications of diabetes can be.
15	it's perfectly clean. You don't know who's	15	A. Sure.
	reviewing, and so as a reviewer you can be	16	Q. First off, am I correct there are
17	perfectly candid about whether or not you like	17	basically two types of diabetes, type 1 and type
18	the science.	18	2?
19	Q. And have you yourself published any	19	A. Yes, there are other types that are much
20	articles in peer-reviewed scientific journals?	20	less common. Type 1 and type 2 are the two main
21	A. Yeah.	21	ones.
22	Q. About how many?	22	Q. Can you briefly describe what type 1 and
23	A. About 150.	23	type 2 diabetes is?
24	Q. Of those 150, how many had to deal with	24	A. Sure. Type 1 is the less common type.
25	diabetes?	25	About 5 percent of diabetes cases in the U.S. end
	Page 47		Page 49
-	Page 47	-	Page 49
1	A. The majority; 120 or so.		up being called type 1. That's the type that
2	A. The majority; 120 or so.Q. Are you a peer reviewer yourself for any	2	up being called type 1. That's the type that kids and young adults tend to get. They can be
2 3	A. The majority; 120 or so.Q. Are you a peer reviewer yourself for any scientific journals?	2 3	up being called type 1. That's the type that kids and young adults tend to get. They can be quite thin and active. And the problem there is
2 3 4	A. The majority; 120 or so.Q. Are you a peer reviewer yourself for any scientific journals?A. Yeah, for many journals.	2 3 4	up being called type 1. That's the type that kids and young adults tend to get. They can be quite thin and active. And the problem there is an inflammation of the cells in the pancreas that
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2 3 4 5 6	 A. The majority; 120 or so. Q. Are you a peer reviewer yourself for any scientific journals? A. Yeah, for many journals. Q. For how many? A. Fifteen or so. 	2 3 4 5 6	up being called type 1. That's the type that kids and young adults tend to get. They can be quite thin and active. And the problem there is an inflammation of the cells in the pancreas that secrete insulin. Insulin is a key hormone in the regulation of metabolism. And when those cells
2 3 4 5 6 7	 A. The majority; 120 or so. Q. Are you a peer reviewer yourself for any scientific journals? A. Yeah, for many journals. Q. For how many? A. Fifteen or so. Q. And what are national advisory 	2 3 4 5 6 7	up being called type 1. That's the type that kids and young adults tend to get. They can be quite thin and active. And the problem there is an inflammation of the cells in the pancreas that secrete insulin. Insulin is a key hormone in the regulation of metabolism. And when those cells are inflamed, they cease to work, the body loses
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		Page 50		Page 52
	1	Q. Is there scientific evidence	1	respect to whether or not Zyprexa causes type 1
	2	demonstrating that Zyprexa is associated with an	2	diabetes, right?
	3	increased risk of type 2 diabetes?	3	A. No.
	4	A. I believe there is, yes.	4	Q. And you are not a physiologist, are you?
	5	Q. Am I correct that there is not any type	5	A. That's correct, I am not.
	6	of evidence linking Zyprexa with type 1?	6	Q. Which means that you're not somebody who
	7	A. There is some data linking Zyprexa to	7	specializes in conducting studies to evaluate the
	8	ketoacidosis, which is one of the hallmarks of	8	mechanisms by which diabetes occurs?
	9	type 1, but the bulk of evidence that I found was	9	A. That's right.
	10	in relation to type 2 diabetes.	10	Q. So, for example, you've not done studies
	11	Q. Before we talk about the linkage between	11	which would look at clamp studies to look at
	12	Zyprexa and type 2 diabetes, let's talk in detail	12	whether a drug might affect a pancreas, for
	13	about just what type 2 diabetes is and how it	13	example?
	14	develops.	14	A. That's correct.
	15	And have you prepared some slides	15	Q. And I also am correct in saying that
	16	to show the jury that will help us explain what	16	you're not a psychiatrist?
	17	type 2 diabetes is?	17	A. That's right.
	18	A. I have.	18	Q. You don't run a psychiatric clinic?
	19	Q. Okay. The first one is entitled	19	A. No, I do not.
	20	MR. SUGGS: Hard to hear me or	20	Q. And you don't make the risk-benefit
	21	the	21	analyses that psychiatrists and other physicians
	22	THE COURT: Ladies and gentlemen,	22	might make in deciding whether to prescribe
	23	are you having trouble hearing the witness?	23	antipsychotic medications?
	24	Thank you very much for moving the	24	THE COURT: Mr. Suggs.
	25	microphone. See if that cures it.	25	MR. SUGGS: Your Honor, I think
		Page 51		Page 53
	1	Q. (BY MR. SUGGS) The first slide that you	1	this goes beyond the scope of what's
	2	prepared is called Type II Diabetes Mellitus.	2	necessary to
	3	Did I pronounce that right it's mellitus or	3	THE COURT: So do I.
	4	mellitus?	4	MR. KANTRA: Just establishing the
	5	A. It can go either way. I say mellitus.	5	boundaries, sir. With that, my only objection
	6	It's from words meaning sweet urine. Diabetes is	6	would be that he be offered as an expert witness
	.7	from a word meaning outflow, and mellitus is from	7	with respect to type 2 diabetes and not type 1,
	8	Latin meaning sweet. That's how in the days	8	since he's not offering that.
	9	before laboratories, the condition was diagnosed	9	THE COURT: Any objections to that
	10	as sweet-tasting urine or urine that would	10	clarification?
	11 12	attract flies.	12	MR. SUGGS: No, Your Honor.
	13	THE COURT: Mr. Suggs, before we go further, I assume you're offering the doctor as	13	THE COURT: Then I'll recognize him as that, as an expert and will be discussing type
	14^{13}	an expert in the field of diabetes?	14	2 diabetes.
	15	MR. SUGGS: Yes, Your Honor.	15	MR. SUGGS: Your Honor, the State
	16	THE COURT: Any objection or any	16	takes the position that Dr. Brancati is clearly
	17	MR. KANTRA: As what?	17	an expert with respect to both types of diabetes.
	18	MR. SUGGS: As an expert in the	18	We're offering his testimony about type 2 and
	19	field of diabetes.	19	that's essentially you've heard all the
	20	MR. KANTRA: I just have a couple	20	testimony we're going to have about type 1.
	21	questions, if I might.	21	THE COURT: Okay. I will recognize
	22	VOIR DIRE EXAMINATION	22	him for that purpose.
	23	Q. (BY MR. KANTRA) Dr. Brancati, you're	23	MR. SUGGS: Thank you, Your Honor.
	24	not here today to offer an opinion with respect	24	THE COURT: Go, on Mr. Suggs.
1	~ -			

25to a reasonable degree of medical certainty with25Q.(BY MR. SUGGS) Okay. We were talking

14 (Pages 50 to 53)

	Page 54		Page 56
1	about diabetes mellitus, and I believe you said	1	fails to compensate. It's still secreting a lot
	it was originally called sweet water?	2	of insulin, just not enough required for that
3	A. Sweet urine. That's where the name	3	individual to keep glucose levels steady. Then
4	comes from.	4	the blood sugar rises and a bit of a vicious
5	Q. Sweet urine. You say it was diagnosed	5	cycle steps in, because as blood sugar rises, the
6	in the olden days by tasting urine?	6	function of those insulin-secreting cells becomes
7	A. Uh-huh, believe it or not.	7	less efficient, so they secrete a little less
8	Q. Thank you. Glad I didn't have that job.	8	insulin. A little less insulin, a little higher
9	You note there that type 2 is by	9	sugar; a little higher sugar, a little less
10	far the most common in the U.S. How common is	10	insulin; vicious cycle and then diabetes
	it, sir?	11	1
12	A. There current estimates is that there	12	Q. Are there early symptoms of type 2
13	are about 20 million individuals in the United	13	diabetes?
14	States with diabetes and about 90 percent of	14	A. There are.
15	those, 9-0, are thought to have type 2 diabetes.	15	Q. And did you prepare a slide that shows
16	Q. Can you track us through the bullet	16	what those symptoms are as well?
17	points and explain what you've prepared for us?	17	A. I did.
18 19	A. As I've said a moment ago, type 2	18 19	Q. What are the early symptoms of type 2 diabetes?
20	typically occurs in middle-aged, overweight, inactive people. The conventional wisdom is that	20	A. So this this slide lists a variety of
20	this is the typical sequence of events. That you	20	symptoms. Many people will have some and some
	have someone who starts off as a young adult who		will have all, depending on their particular
	is lean and active, and they gradually gain		circumstances. So one of the cardinal signs is
	weight as they go towards middle age. And weight		increased urine production. People will notice
	gain because of increased calorie intake and	25	that they're urinating more frequently, that the
	Page 55		Page 57
1	decreased calorie expenditure in the form of	1	volume of the urine is larger each time they go,
2	exercise and so weight deposits and then that	2	that if they've not been urinating at night, they
3	weight gain is associated with insulin	3	might notice they're getting up at night. If
4	resistance.	4	they have been, they might notice that they're
5	Q. Sorry. I was going to ask you what	5	getting up more or the volumes at night are
6	insulin resistance is.	6	greater.
7	A. Sure, sure. Well, for the body to	7	As fluid goes through the body,
8	maintain a stable label of glucose, the pancreas	8	they become thirsty. The fluid intake the
9	serves as a bit of thermostat. It senses the	9	body prompts the person with diabetes to consume
10	level of glucose or sugar in the blood. As that	10	more fluid to stay even and stave off
11	level rises, the pancreas secretes insulin. And	11	dehydration.
12	then the response of the body depends on a prompt	12	The other thing that happens
13	response to the insulin-sensitive tissues to that	13	because calories are flowing out in the urine.
14 15	signal.	14	Now the sugar that goes out in urine, that's real
	What happens is as people gain	15	calories. It starts to pull calories from the
16 17	weight and reach middle age is they'll develop resistance to that insulin signal or it will take	16 17	body, and that will lead to increased hunger as if the individual had been exercising and burning
18	more and more insulin to generate the same	18	calories that way. So people will report
19	response of the body to incorporate glucose from	19	increased hunger and they're eating more, but
20	the blood into the insulin-sensitive tissues like	20	ironically they're more hungry, they're eating
21	fat and liver and muscle. As long as the	21	more, but they'll have weight loss. Some of that
			•
22	-	22	weight loss is from the calories going out in the
22 23	pancreas compensates by making more insulin, by	22 23	weight loss is from the calories going out in the urine. Some of the weight loss is fluid that's
23	-		weight loss is from the calories going out in the urine. Some of the weight loss is fluid that's going out being pulled along with the glucose.

	Page 58		Page 60
1 th	ney become a little dehydrated, they might feel	1	Q. Let me stop you for a second there.
	atigued, malaise, they don't feel right. They	2	That 126 milligrams per deciliter, that's 126
	on't know exactly what it is. Those are often	3	milligrams of glucose in a certain volume of
	ne complaints that bring them into the doctor's	4	blood?
	ffice. A lot of people like the unexplained	5	A. Yes. A deciliter is a tenth of a liter.
	reight loss because remember, this is going on in	6	Q. Okay. And what's the second one listed
	eople who are overweight. They often interpret	7	there? The second test?
8 it	as an unusually successful diet.	8	A. The second one listed there is used most
9	So they get fatigue, malaise. Then	9	often in research studies. This is a definition
10 as	s their fluid levels drop, they can become	10	based on an oral glucose tolerance test. This is
	ghtheaded. And the high levels of sugar and		used most commonly in clinical practice in the
	ne shifting levels of sugar in the body can		United States for pregnant women, otherwise we
	ffect the way the lens of the eye works and lead		don't do many glucose tolerance tests. The idea
	blurred vision.		there is that if you want to pull out all the
	Q. And is it these symptoms that usually	15	stops to make the diagnosis, you don't rely only
	rings a patient into the doctor's office?		on the fasting glucose, because that can hide
	A. Yes.	17	levels of hyperglycemia occurring during the rest
	Q. Okay. When they do go to the doctor's	18	
	ffice, how do you go about have you prepared	19	So what's done in the oral glucose
	slide showing how diabetes is diagnosed?		tolerance test is you give the patient a very
	A. I have.		sweet drink that is very syrupy, about 75 grams
	Q. Okay. And how do how do physicians	22	of sugar in it. They swig that and you measure
	iagnose type 2 diabetes?	23	the blood sugar just before they drink it, and
	A. There are at least three ways. And I'll tart at the bottom here because it ties in with	24	you wait two hours later and measure again. If
25 St		25	they don't meet the fasting criteria for
	Page 59		Page 61
	ne symptoms. For someone who comes into the	1	diabetes, they could still meet it in two hours.
	octor's office complaining of increased urine,	2	In someone who doesn't have diabetes, two hours
	nirst, hunger, unexplained weight loss, fatigue	3	after the oral glucose is taken, their blood
	nd so on, all the classic symptoms, if a blood	4	sugar should be less than 200. If it's 200 or
	est is drawn that shows that the glucose or the	5	greater, that's evidence of diabetes. Diabetes
	ugar level in the blood is greater than or equal	0	you may not have found just by testing the
	200 milligrams per deciliter, that's a	8	fasting sugar.
	oncentration in the blood and they have these vpical symptoms, that makes a diagnosis. And it	9	Q. Thank you. Do you have some slides that show how the body converts food to sugar and the
	oesn't matter whether the blood was drawn first	10	role of insulin in this process?
	ning in the morning before they ate or late in	11	A. We do.
	he afternoon, after breakfast and lunch. That's	12	Q. Okay. I notice that this slide has a
	lenty of evidence and that's how most people	13	legend down on the bottom that says, Look Ahead,
1	vith diabetes in the United States are diagnosed	14	Action for Health and Diabetes. What's that
	clinical practice.	15	mean?
16 II	There are two other ways to make	16	A. This was a slide I took from one of the
	ne diagnosis in the absence of symptoms. All of	17	
	nem rely on blood tests. One is to do a fasting	18	test this is a study, ongoing study designed
	lood test. This is first thing in the morning		to determine the long-term health benefits of
	fter fasting for 10 or 12 hours. Under those	20	weight loss in people with diabetes. We have a
	ircumstances, the concentration of sugar,	21	teaching module in the trial for the purposes of
100 -1		22	bringing people with diabetes up to date, and
22 gl	lucose in the blood should be less than 126		
23 m	nilligrams per deciliter. If it's 126 or higher,	23	this is one of the figures that we use.
23 m 24 th		23 24	

	Page 62		Page 64
1	not talking about us today, right?	1	stomach. We usually don't think about it much.
2	THE WITNESS: That's correct. In		Much of the substance of the pancreas is devoted
3	scientific medical jargon, a trial is an	3	to making pancreatic juices, enzymes that help
4	experiment in humans, and typically the design is	4	digest foods, especially fat. But if you slice
5	you take a group of people at risk for some		it and look under a microscope, you see small
6	complication. In the case of Look Ahead, we have	6	islands of cells.
7	people with diabetes at risk for heart disease.		They're actually called islet
8	We flip a coin and assign half the study		cells. And they're the insulin-secreting cells
9		9	of the pancreas. They're very well-positioned to
	participants to one condition. In this case, it's just their usual care. And we flip a coin	-	
10		10	sense the levels of sugar in the blood and so
11 12	and assign the other group of individuals to		they're poised to respond quickly. When the
13	another question and Look Ahead, it's intensive		sugar level goes up, the insulin secreted by the
14	coaching about weight loss.	13	pancreas the insulin goes all over the body
	And then the trial component, you	14	through the blood supply. And it specifically
15	follow both groups forward over time and you look	15	triggers three types of tissue to take sugar or
16	for systematic differences in the occurrence of	16	glucose out of the blood and into that organ.
17	those complications.	17	And those insulin-sensitive organs are liver,
18 19	THE COURT: Thank you.		muscle and fat, fat all over the body.
	MR. SUGGS: Thank you, Your Honor.	19	Q. How is it that insulin regulates the
20	Q. (BY MR. SUGGS) This chart shows at the	20	activity of sugar or the presence of sugar?
21	top, food in the form of carbohydrates going into	21	A. For these three types of organs, sugar
22	the stomach and then apparently getting converted	22	can't get into can't get from the bloodstream
23 24	to sugar.		into the organ without insulin more or less
	Is it only carbohydrates that are	24	unlocking the door.
25	used by the body to make sugar?	25	Q. Do you have a slide showing that?
	Page 63		Page 65
1	A. We show carbohydrates here because	1	A. Oh, yes. Yes, I do. So, in fact,
2	that's the constituent of the diet that's most	2	here's the lock and the key. These are fat
3	directly converted to glucose, but the liver,	3	cells, a rim of cell, and then a big fat droplet
4	part of the liver's job in the body is to be a	4	on the inside. This is sort of the way they look
5	clearinghouse for all different types of food		under the microscope. And even if there's sugar
6	substances. And part of what the liver does is	6	bathing that tissue, it won't go in unless
7	it can take protein, convert it to carbohydrate;	7	there's insulin there to send a signal to the
8	take carbohydrate, convert it to protein; convert	8	cell to actively take the sugar from the
9	both of those to fats. That's the liver's job	9	bloodstream into the fat cell. If there's no
10	but we just show carbohydrate here as an example.	10	insulin circulating, as in kids with type 1
11	Q. Can you walk us through the chart	11	diabetes, who get inflamed pancreases, that's a
12	starting at the top, and how the body processes	12	problem where sugar will build up in the
13	food.	13	bloodstream and cause diabetes.
14	A. Sure. So this is north in the body.	14	In people with type 2 diabetes,
15	This is south, so people eat food, it goes into	15	there's plenty of insulin floating around. The
16	the stomach. It's acted on by digestive enzymes	16	trouble is some of the keyholes are blocked and
17	and for carbohydrates that releases a lot of	17	it doesn't signal properly and the sugar backs up
18	sugars into the blood system. So this tube here	18	into the blood supply for that reason.
19	represents the blood system around the gut. The	19	Q. And what is it that makes those cells
20	S's represent molecules of sugar or glucose. The	20	resistant to insulin?
21	I represents molecules of insulin.	21	A. That's a great question. There's still
22	When sugar is released into the	22	a lot of active research on that but we know a
	bloodstream, that signals the pancreas to act.	23	lot more than we did ten years ago. When I was
23			
23 24 25	This is the pancreas, it's about the size of your fist, and it sits back behind the pit of the	24 25	coming through training, the thought was that, for example, fat tissue was really inert. It was

	Page 66		Page 68
1	just a storage depot, just a place to keep energy	1	A. Yes, in the majority of cases, those
2	in the form of fat and, you know, wasn't	2	elevations of blood sugar in middle-age,
3	otherwise very active in regulating the metabolic	3	overweight individuals is related to the insulin
4	machinery of the body.	4	resistance.
5	Now we know that the fat cells	5	Q. Is when the blood has higher levels
6	secrete a variety of hormone-like substances,	6	of sugar in it than normal, is that referred to
7	small molecules called adipocytokines. They flow	7	as hyperglycemia?
8	out of the fat cells into the blood. They	8	A. Yeah, hyperglycemia can refer to
9	circulate around the body and they change a	9	increases in blood sugar across a whole range.
10	variety of things. They can change behavior.	10	So, for example, in the general population a
11	They can influence appetite. They can influence	11	normal level in a middle-age adult might be 85 or
12	the way the liver responds to insulin levels.	12	
13	They can affect the way the fat cells themselves	13	90 to 105, they're showing some degree of
14	respond to insulin.	14	hyperglycemia because it's high compared to where
15	So there's intense interest now in	15	they were or it's high compared to a normal
16	identifying those molecules, and there are many	16	population.
17	of them, in an attempt to develop drugs that	17	By the same token, if you talk to
18	might influence the way fat leads to insulin	18	an endocrinologist, 105, that's great control for
19	resistance.	19	someone with diabetes. Hyperglycemia in kids
20	Q. So weight gain, is that related to	20	with diabetes might be 300 or 400. It all
21	insulin resistance?	21	depends on where you're starting. Hyper,
22	A. Yeah. So a lot of evidence from a	22	depending on the study or setting, means higher
23	variety of sources that weight gain or adiposity	23	than expected or higher than before or too high
24	itself people who are already overweight or		for safety.
25	obese, that those individuals are much more	25	Q. I've heard doctors sometimes talk about
	Page 67		Page 69
1	likely to have insulin resistance than leaner	1	Page 69 signs and symptoms. What's the difference
1 2	likely to have insulin resistance than leaner individuals.	1 2	signs and symptoms. What's the difference between the sign and the symptom?
	likely to have insulin resistance than leaner individuals. Q. Okay. And is it fair to say that if the	1 2 3	signs and symptoms. What's the difference between the sign and the symptom? A. A symptom is a complaint, so that
2 3 4	likely to have insulin resistance than leaner individuals.Q. Okay. And is it fair to say that if the body becomes insulin resistant, the sugar that's	2 3 4	signs and symptoms. What's the difference between the sign and the symptom? A. A symptom is a complaint, so that depends on the judgment of the patient. And
2 3 4	likely to have insulin resistance than leaner individuals.Q. Okay. And is it fair to say that if the body becomes insulin resistant, the sugar that's in the bloodstream does not make it into the fat	2 3 4 5	signs and symptoms. What's the difference between the sign and the symptom? A. A symptom is a complaint, so that depends on the judgment of the patient. And given the same sort of physical conditioning
2 3 4 5 6	likely to have insulin resistance than leaner individuals.Q. Okay. And is it fair to say that if the body becomes insulin resistant, the sugar that's in the bloodstream does not make it into the fat cells and just remains circulating in the	2 3 4 5 6	signs and symptoms. What's the difference between the sign and the symptom? A. A symptom is a complaint, so that depends on the judgment of the patient. And given the same sort of physical conditioning physical condition, two patients may have very
2 3 4 5 6 7	likely to have insulin resistance than leaner individuals.Q. Okay. And is it fair to say that if the body becomes insulin resistant, the sugar that's in the bloodstream does not make it into the fat cells and just remains circulating in the bloodstream?	2 3 4 5 6 7	signs and symptoms. What's the difference between the sign and the symptom? A. A symptom is a complaint, so that depends on the judgment of the patient. And given the same sort of physical conditioning physical condition, two patients may have very different symptoms. Someone who is very stoic
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$\begin{array}{c} 2\\ 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 9\\ 20\\ 22\\ 23\\ 24\\ \end{array}$	 likely to have insulin resistance than leaner individuals. Q. Okay. And is it fair to say that if the body becomes insulin resistant, the sugar that's in the bloodstream does not make it into the fat cells and just remains circulating in the bloodstream? A. Exactly. So that's what's thought to happen when you see blood sugars rise from the normal range, which might be in the 80 to 90 range. And they they rise they can rise to 100, 105, 110 as still not in diabetic range, but now in that 100 to 125 range which we call impaired fasting glucose. Those are individuals who seem to be on their way to getting diabetes, and it's a high-risk group that's been targeted by public health agencies and the federal government in diabetes prevention strategies. Q. Earlier you were talking about the diagnosis of diabetes by looking at the blood levels of sugar. Is it fair to say that those elevated blood levels then are the result of 	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	 signs and symptoms. What's the difference between the sign and the symptom? A. A symptom is a complaint, so that depends on the judgment of the patient. And given the same sort of physical conditioning physical condition, two patients may have very different symptoms. Someone who is very stoic will have no symptoms even if they're having terrific metabolic derangements. A sign is something objective measured by the physician. Could be a physical sign, something they find on exam. The skin is dry, the membranes of the mouth are dry and make a diagnosis of dehydration, or could be it could be from examining the chest with a stethoscope. Those sorts of things are signs. Q. Okay. And is hyperglycemia a sign of diabetes? A. Yes. So you can also have signs that are obtained by laboratory assessment, kind of an extension of the senses of the physician.

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1 anything other than diabetes?	1 blood vessel disease we can see in vessels
2 A. No, unless they happen to be in the	2 vessels we can see with the naked eye. We can
3 hospital and have glucose running intravenously	³ see the disease with the naked eye. So when we
4 and have some external source of blood sugar then	4 go to medical school and we dissect, we learn.
5 in clinical practice it's really diabetes	5 We can see the vessels of the heart, the coronary
6 mellitus.	6 arteries; we can see the vessels that lead to the
7 Q. Thank you. So would it be fair to say	7 brain, the carotid arteries; and the vessels that
8 that if you did a randomized study where you gave	8 lead to the leg, the femoral arteries. And
9 one group of patients a particular treatment and	9 macrovascular disease is the term that diabetes
10 after that they then showed that group showed	10 researchers use for what other physicians and
11 hyperglycemia, what would you what would you	11 researches call athersclerosis or blockage of the
12 take from that?	12 arteries from cholesterol deposits, inflammation
13 A. If it's hyperglycemia in the frankly	13 and superimposed clot.
14 diabetic range, 126 or greater, then I'd conclude	14 Q. And is there a higher incidence of
15 that the drug is provoking episodes of of	15 macrovascular disease in diabetes?
16 diabetes. If it's if it's hyperglycemia,	16 A. Yes, there sure is. Macrovascular
17 still in the nondiabetic range, it would make me	17 disease can occur and does occur in people
18 worry that the drug is pushing individuals from a	18 without diabetes. The trouble with the
19 normal state to insulin resistant to impaired	19 problem for people with diabetes is that they
20 fasting glucose on the way to diabetes, but maybe	20 have a much accelerated process compared to
21 not yet.	21 nondiabetic individuals. They are at much higher
22 Q. We talked about how hyperglycemia occurs	22 risk.
23 in diabetes. Why do we care if somebody is	23 Q. And do we know why that is?
24 hyperglycemic? What's the result of having too	24 A. A lot of different theories, but like
25 much sugar in the blood?	25 everything else related to diabetes, it's
	3 8 9
Page 71	Page 73
1 A. Well, I mentioned some of the short-term	1 multifactorial. Some of the theories have to do
2 problems which could be troublesome, but the real	2 with modification of the cholesterol which is
3 problems is with diabetes in general type 2	3 involved in creating the blockage so that it's
4 diabetes, in particular, are the long-term	4 more likely to deposit. Another line of
5 vascular complications, the damage to the large	5 reasoning has to do with inflammation inside the
6 and the small vessels in the body.	6 body, really around the body in such a way that
7 Q. Do you have a chart or slide rather,	7 the that the smooth lining of the blood vessel
8 that summarizes that?	8 is damaged or creates an area for deposition of
9 A. Ido.	9 cholesterol.
10 Q. Actually, before we get to that I	10 Another theory has to do with the
11 take it back, let's go right there.	11 effects of high blood sugar on platelets, the
12 This slide that you prepared is	12 small elements in blood that are involved in
13 entitled, Diabetes Leads to Long-term Health	13 forming clots. So there's a variety of different
14 Problems and Death by Damaging Blood Vessels.	14 pathways to atherosclerosis.
15 And you've got two headings in there. The first	15 Q. You've used the term atherosclerosis now
16 is macrovascular disease.	16 a couple of times. Do we have a chart or
17 Can you explain what you mean by	17 actually a picture that shows that process?
18 that phrase macrovascular disease?	18 A. We do.
19 A. Well, let me make the contrast between	19 Q. Can you tell us what this depicts?
20 macro and micro. Macro is a prefix that means	20 A. Sure. So this is a cross-section of,
21 big or visible to the naked eye in this case;	21 say, a coronary artery. So this would be if you
22 micro means small or too small to be seen by the	22 have the artery like this and snip it and look at
23 naked eye. You need a microscope. And vascular	23 it down longways into the opening. This is what
24 means blood vessels, or the tubes that carry	24 VOUG CAAIN A NORMAL VACCAL THRAA LAVARC OF
25 blood. So macrovascular disease is the type of	24 you'd see in a normal vessel. Three layers of25 tissue here, the endothelium here and the blood

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1	would pass through the lumen or the open part.	1	Q. Okay. And can this atherosclerosis
2	You see here it's nice and clear and the blood	2	occur anywhere in the body?
3	can pass through at high speed.	3	A. It can occur anywhere. We're most
4	What happens in atherosclerosis is	4	concerned about when it occurs in crucial
5	that there's damage to that lining, to that	5	vascular beds, the blood vessels that lead to key
6	endothelium. And then inflammation around it.	6	organs. The three most important and commonly
7	That brings inflammatory cells to the area, cells	7	affected are the brain. When you get this in the
8	that attract cholesterol and various other	8	vessels that lead to the brain, you can get
9	material. The cholesterol begins to deposit,	9	stroke. When it occurs in vessels that feed the
10	first at the inflamed site and then all around	10	heart, you get heart attack and when it occurs in
11	the vessel. You can see as this plaque forms,	11	vessels that go to the legs, first you can get
12	this area of gunk underneath the endothelial	12	claudication, pain with walking, but then that
13	lining, the lumen, the open part of the vessel	13	can progress all the way to gangrene and the need
14	begins to contract markedly. Now whatever is	14	for limb amputation.
15	downstream from that vessel is at risk because	15	Q. Okay and did you bring some slides that
16	the body can't deliver blood and oxygen and	16	show atherosclerosis in the heart?
17	nutrients to the same extent as before.	17	A. I did.
18	This might be the case in someone	18	Q. Will you turn to that next. Can you
19	with chronic stable angina. So take someone who	19	describe for the jury what this depicts?
20	says that when they're at rest they feel fine.	20	A. Sure. Here are some of the here's
21	They go up one flight of stairs, they're okay.	21	the heart and this is the meaty part of the
22	Try two or three flights, they get short of	22	heart, the chamber that does the pumping, and it
23	breath, chest discomfort, they get winded. That	23	has three main vessels that feed it. And here's
24	would be the circumstance here. They can only	24	a diagram of one of those vessels and this shows
25	deliver so much blood and oxygen to the heart.	25	the development of atherosclerosis in the vessel.
	Page 75		Page 77
T	As soon as they're below that requirement,	1	Now, instead of looking at the vessel end on,
⊥ 2	As soon as they're below that requirement, they're okay. As soon as they push beyond it,	1 2	it's been unroofed and you're looking along the
1 2 3	they're okay. As soon as they push beyond it, they get symptoms.	1 2 3	it's been unroofed and you're looking along the long axis of the vessel and this is what you
2 3 4	they're okay. As soon as they push beyond it, they get symptoms. That's bad; but this is worse.	2	it's been unroofed and you're looking along the long axis of the vessel and this is what you could see with the naked eye. You'd see this
2 3 4 5	they're okay. As soon as they push beyond it, they get symptoms. That's bad; but this is worse. Here's the plaque and now there's a plug of clot	2 3 4 5	it's been unroofed and you're looking along the long axis of the vessel and this is what you could see with the naked eye. You'd see this yellowish, cholesterol-laden plaque constricting
2 3 4 5 6	they're okay. As soon as they push beyond it, they get symptoms. That's bad; but this is worse. Here's the plaque and now there's a plug of clot right over it. This is what happens in someone	2 3 4 5	it's been unroofed and you're looking along the long axis of the vessel and this is what you could see with the naked eye. You'd see this yellowish, cholesterol-laden plaque constricting the lumen or the open part of the vessel. And in
2 3 4 5 6	they're okay. As soon as they push beyond it, they get symptoms. That's bad; but this is worse. Here's the plaque and now there's a plug of clot right over it. This is what happens in someone who has a heart attack, or the technical term is	2 3 4 5	it's been unroofed and you're looking along the long axis of the vessel and this is what you could see with the naked eye. You'd see this yellowish, cholesterol-laden plaque constricting the lumen or the open part of the vessel. And in this diagram there's a clot there. So this is
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	Page 78		Page 80
1	That's what a coronary artery bypass surgery is,	1	And then you typically see this wedge-shaped
2	or coronary surgery is.	2	triangular area of stroke or death because all
3	Another approach is to lead a small	3	the branches of the vessel downstream will be
4	plastic catheter tube from the leg, up into the	4	occluded and the part of the brain fed by those
5	vessels, back into the vessels, and then inflate	5	vessels will die.
6	a balloon inside the blocked area. The balloon	6	Q. Okay. And I believe you said also that
7	presses the plaque up against the side walls of	7	this type of atherosclerotic process can also
8	the vessel, opens it up more. That's	8	affect limbs; is that correct?
9	angioplasty. And typically today, following	9	A. That's correct, especially the legs.
10	angioplasty there's stenting, which is the	10	Q. And do we have a diagram that shows that
11	placement of a small metal coil or mesh in the	11	as well?
12	area that's been ballooned to keep it open.	12	A. We do.
13	Q. You said this type of process could	13	Q. Tell us what is shown on these pictures.
	result in a heart attack. I've also heard the	14	A. Here's the leg. Here's the femoral
15	expression myocardial infarction or MI. Is there	15	artery. This is if your doctor's ever felt for
16	any difference there?	16	the pulse down in the groin, they're feeling up
17	A. All the same.	17	here. They're feeling the pulsation through that
18	Q. In the myocardial infarction or the	18	artery. It's a big one. Normally it's wide open
19	heart attack, is that where the blood vessel gets	19	and it needs to convey a lot of blood and
20 21	plugged up with the clot like we saw in the other	20	nutrients, but the leg is a big chunk of tissue
21	diagram?	21 22	and quite active. When atherosclerosis occurs,
23	A. Exactly. And then everything downstream from that from that plaque and clot is at risk	23	there's blockage of that big vessel. It's big enough that there's no the first people will
23	and will be initially stunned and then deprived	24	get is pain or limping or cramping with exercise.
25	of blood and oxygen, will actually die off and	25	So someone will say, when I'm at rest, it's fine,
15	Page 79		
			Page 81
1		1	Page 81 when I'm walking slowly for a block it's fine
1 2	scar.		when I'm walking slowly for a block, it's fine
2	scar. Q. Okay. You said that also this process	1 2 3	when I'm walking slowly for a block, it's fine but if I walk two blocks quickly, my legs will
2 3	scar. Q. Okay. You said that also this process can result in problems with the brain.	2 3	when I'm walking slowly for a block, it's fine but if I walk two blocks quickly, my legs will cramp up. I'll get pain in the calves and I have
2	scar. Q. Okay. You said that also this process		when I'm walking slowly for a block, it's fine but if I walk two blocks quickly, my legs will cramp up. I'll get pain in the calves and I have to rest for five minutes, then I can walk again.
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 20 21 22	 scar. Q. Okay. You said that also this process can result in problems with the brain. Do you have a slide showing that as well? A. I do. Q. What does this slide depict? A. So here's a cross-section of the brain. This is the neck and the ears and the head. The carotid artery comes from the heart, from the aorta down here. There are two main carotid arteries, one on each side of the neck. You can feel if you press, the pulse here. That artery tends to develop atherosclerosis. When it does, it can cause trouble in two ways. One is that if clot forms on top of the plaque, the brain downstream from the carotid down from the blockage will die and that's called a stroke. So that can happen either because of a blockage down here or it can happen because a small clot forms, blood clot can pass here, but the clot breaks off, runs upstream 	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	when I'm walking slowly for a block, it's fine but if I walk two blocks quickly, my legs will cramp up. I'll get pain in the calves and I have to rest for five minutes, then I can walk again. Q. What is the end stage of this particular problem in the leg? A. The problem here is that the leg gradually becomes more and more ischemic. It's getting less and less blood and less and less oxygen. And that that predisposes to infection and infection can be very severe if the blood if the body is unable to deliver oxygen and nutrients and inflammatory cells to the involved area. As the blood supply is closed off, there could even be death of the tissue downstream. So death of tissue due to lack of blood is called gangrene. There's dry gangrene when there's no infection involved and it's just lack of blood and oxygen that kills the tissue; it's called wet gangrene when there's an active infection along with the compromised blood supply.

	Page 62		Page 04
1	Q. And what is this picture showing?	1	leg. It turns out to be the leg that's affected
2	A. This is the foot of someone with	2	because those nerves are the longest. They go
3	diabetes. You see here the tips of the toes and	3	from the spinal cord all the way down to the leg.
4	in this case the entire toe has essentially just	4	So they're more vulnerable to lack of blood
5	died, turned black, and gradually worn worn	5	supply, oxygen and nutrients. Neuropathy can
6	- · ·	6	
7	away because of lack of blood supply.	7	first lead to pain in the absence of any sort of
	Q. Okay. So we've now talked about	8	pressure. For example, the type of pain that
8	atherosclerosis in the big vessels that can		people get with shingles, it's a nerve pain.
9	impact the heart, the brain and the limbs.	9	Very troublesome. Then there also could be
10	Have we covered the macrovascular	10	sensation loss, which is ironic given they could
11	side of the problem?		have pain but also lose a sensation. So the big
12	A. Yes.		worry in people with severe diabetic neuropathy
13	Q. Okay. Let's go back and take a look at	13	is they'll step on a nail and not notice it until
14	the microvascular side of this.	14	the foot's infected. So the sensation loss can
15	This is the slide we looked at	15	be that profound.
16	earlier. But could you focus on the	16	And then the sensation loss, the
17	microvascular portion of the slide and describe		risk of trauma and injury to the leg and the
18	for us what is involved in microvascular disease?	18	likelihood they may not find infections early
19	A. Sure. Macro is you can see with the	19	when they happen all predispose to serious
20	naked eye. Microvascular disease is disease of	20	infection, gangrene and limb loss.
21	the small vessels; the ones you can only see with	21	Q. Let's focus on the retinopathy or the
22	the microscope. There are three vessel beds we	22	blindness part of it first. Let me pull up
23	are particularly concerned about in diabetes; the	23	another slide and can you describe for us what's
24	retina, which is the screen in the back of the	24	involved some more detail with respect to
25	eye that lets us see; the kidney and the nerves,	25	-
	Page 83		Page 85
1	especially the nerves of the leg. One thing	1	A. Sure. As I mentioned, hyperglycemia or
2	that's different about micro versus macrovascular	2	high blood sugar is the culprit here, the small
3	disease, not only which vessels are infected, but	3	vessels, the microscopic vessels of the retina.
4	how typical it is of diabetes. Nondiabetic	4	If it causes some damage directly, it damages the
5	individuals get macrovascular disease all the	5	wall of those vessels so they get, on the one
6	time. It's just very accelerated in diabetes.	6	hand leaky, on the other hand blocked. So the
7	Microvascular disease really occurs	7	retina the retina experiences a loss of
8	only in people with diabetes. You don't see this	8	oxygen. It attempts to compensate by growing out
9	kind of damage in people who don't have diabetes.	9	new vessels to bring in blood supply around those
10	The main reason is that because the bad actor is	10	blockages. The trouble is that the new vessels
11	the high blood sugar causing damage to these	11	are really quite fragile and they don't grow just
12	vessel beds. When high blood sugar damages the	12	in places where they should grow, so it creates
13	small vessels of the retina, we call that	13	problems for the eye. It's an adaptation that
14	retinopathy. Pathy just means disease, so it's	14	turns out to be dangerous. A maladaptation.
15	retinopathy disease of the retina it's	15	And so diabetic eye disease,
16	diabetic and it's the leading cause of acquired	16	diabetic retinopathy can interrupt vision in a
17	blindness in the United States.	17	variety of different ways. The leakage of the
18	Nephropathy or disease of the	18	fluid and the proteins from the vessels, if that
19	kidney due to diabetes. That's the leading cause	19	leakage occurs over the part of the retina
20	of kidney failure in the United States, which	20	problem that's involved in visual acuity called
21	used to be uniformly fatal before dialysis. Now	21	the fovea, that can lead to blindness. The new
22	diabetic nephropathy is the leading cause for	22	vessels grow out; they're very fragile. If they
23	Americans to go on hemodialysis.	23	rupture and bleed and the bleeding occurs over
24	And neuropathy is disease of the	24	the point of visual acuity, over the fovea, you
25	vessels leading to the nerves, especially in the	25	can get blindness from that.
J	vessers reduing to the nerves, especially in the	20	can 50t onnuness nom mat.

	Page of		Page oo
1	The new vessels don't confine	1	Q. Let me interrupt. The sort of orangey
2	themselves to the retina, the movie screen in the	2	color there, that's the retina?
3	back of the eye; they should. Many of them grow	3	A. Yeah, this is the substance of the
4	out to the vitreous, which is the jelly-like part	4	retina. Here's the vein going to the retina.
5	of the eye that forms the bulk of the eye. When	5	Here's the artery. Fresh blood goes out of the
6	those vessels grow out to the vitreous, you can	6	artery, comes back in the vein. This orange
7	have hemorrhage there, so that can just block the		substance here is the rods and the cones, the
8	light from coming in the back. The new vessels	8	part of the retina that lets us sense light and
9	• •	9	see. And where all these arrows go, there's
10	can also tug the retina in such a way that it detaches. And a detached retina can cause	10	other stuff in the retina that shouldn't be
11	blindness. There's also a damage in front of the	11	there. The exudate, the abnormal vessels,
12	eye that can lead to buildup of pressure and	12	microaneurysms and the hemorrhage or the blood in
13	glaucoma and loss of vision from that route as	13	the retina.
14	well.	14	Q. So is the problem with exudate, for
15	Q. Do we have a diagram of the eye that	15	example, is that a problem where the exudate is
16	illustrates those different processes that you're	16	sort of covering the rods and the cones and
17	talking about?	17	preventing the light from impacting those cells
18	A. We do.	18	and being detected?
19	Q. Tell us what this slide shows.	19	A. Yeah, with hemorrhages and exudate, it
20	A. Sure. Here's the eyeball. Here's the	20	can be just physically blocking the light or it
21	front of the eye this way, the back of the eye	21	can be destruction of the underlying tissue by
22	that way and then the brain would be normally	22	poisoning the local environment essentially.
23	back in the back here. Here's the retina, the	23	Q. With respect to the hemorrhage there, is
24	movie screen in the back of the eye. The light	24	that also obscuring the cells that pick up the
25	comes in the front, focused by the lens, goes on	25	light and send those signals to the brain?
	Page 87		Page 89
1	the notine signals nicked up node and some	1	A Again the home where can block the
-	the retina, signals picked up rods and cones,		A. Again, the hemorrhage can block the
2	those cells we learned about in grade school.	∠ 2	light or be directly toxic to the fragile cells
3	They send signals back to the brain and we are	3	in the immediate neighborhood.
4	able to see.		Q. Those little abnormal blood vessels,
5	The retina is the movie screen in	5	what's the problem with those? Why do we care
6	the back. The vitreous is the jelly-like	6	about that?
7	substance between the lens and the retina. This		A. That's the adaptation to the lack of
8	section here shows a small part of the retina,	8	blood supply, because the first thing that
9	and shows all the things that can go haywire.	9	happens is that these arterials are narrowing in
10	Here's an arterial that's been affected by	10	diabetes and the retina is sensing that it's
11	diabetes. One one consequence is that the	11	getting less oxygen than it should. It sends out
12	vessel wall weakens and you get the formation of	12	signals to the blood vessels to grow out, as if
13	microaneurysms these little red spots, outpouches	13	there aren't enough vessels. Unfortunately, when
14	of very tiny vessels. They're not dangerous in	14	people reach childhood and young adulthood, let
15	themselves but they're used by ophthalmologists	15	alone adulthood, those new vessels that grow out,
16	to detect the early ill effects of diabetes.	16	they're not like the old ones. They're not as
17	Then those vessels, as they get	17	good, they're not really functional, they cause
18	leakier and leakier, they can leak out protein,	18	more harm than good, they're small, they're
19	and this whitish material that we call exudate.	19	tangly, they're very fragile.
20	They can also rupture and blood can be released	20	Q. So if they're fragile do they
21	into the substance of the retina, a hemorrhage.	21	hemorrhage?
22	And then these new vessels grow and they're	22	A. Yes, these vessels are at the highest
23	especially predisposed to hemorrhage, and they	23	risk for hemorrhage. Once this occurs once
24	can also pull the retina from its moorings and	24	ophthalmologists detect this, they can see this
24 25	can also pull the retina from its moorings and detach it.	24 25	ophthalmologists detect this, they can see this when they look in the back of the eye. Once they

	Page 90		Page 92
1	detect this they begin laser therapy to knock out	1	send blood say the heart pumps blood to, say,
2	those vessels and sometimes to burn a moat around	2	our legs. It pushes all the nutrients, pushes a
3	the diseased area to prevent it from affecting	3	lot of the fluid out. And then on the return
4	the less of the retina.	4	trip it has to have a way to re-collect the fluid
5	Q. Okay. Because if those vessels do	5	and minerals. The only sort of pressure dragging
6	bleed, then they obscure the rods and cones?	6	the fluid and minerals back is called osmotic
7	A. Damage the cells or obscure their	7	pressure, it's because the protein concentration
8	contact with light from the outside.	8	in the blood of albumin is maintained high enough
9	Q. Okay. Let's talk next about diabetic	9	that it actually sucks that fluid back in. When
10	nephropathy, where the kidney gets damaged. Do	10	albumin levels drop, and the blood goes to the
11	we have a slide that explains that in more	11	leg, the fluid gets pushed out and never comes
12	detail?	12	back and is one of the causes of leg swelling and
13	A. We do.	13	fluid retention in the legs. That happens in
14	Q. If I can get this to work.	14	other parts of the body, for example, the chest
15	MR. SUGGS: It's shooting, but it's	15	and it causes shortness of breath and trouble
16	not	16	there.
17	Okay. I think we went too far.	17	Q. Okay. I interrupted you. Can you go
18	There's one entitled Diabetic Nephropathy I.	18	back and explain what you mean by less filtering?
19	There we go.	19	A. So one problem is the leakiness. The
20	Q. (BY MR. SUGGS) Can you explain to us	20	other problem is sort of not leaky enough. One
21	what's involved with diabetic nephropathy or	21	way to think about this is using a coffee filter
22 23	damage to the kidney?	22	
23 24	A. Sure, well, this is the characteristic	23	leaky and let the coffee grounds go into the pot.
24	damage to the filtering part of the kidney. It's called the glomerulus. It's where the blood		You don't want it that leaky. On the other hand, if the filter doesn't work, if it was made of
25	•	25	
	Page 91		Page 93
1	supply comes in contact with the structures that	1	linoleum, you wouldn't be able to make coffee
2	lead to the urine. And there's microscopic	2	because it needs to filter to a certain extent.
3	damage there that causes two problems kind of in	3	You need a filter that works just right.
4	parallel with what is happening in the retina.	4	Diabetes creates two problems for
5	Those vessels become more leaky is one problem.	5	the kidney. It makes parts of it more leaky and
6 7	And when those vessels are leaky, the blood loses vital proteins out into the urine that should	6	it makes part of it not leaky enough. So the
8	normally be kept in the body, but are wasted in	8	overall amount of filtering that goes on decreases. This is the bigger problem, because
9	the urine and come to the outside world.	9	when there's not enough filtering, the waste
10	Keep in mind, the kidneys are	10	products accumulate in the blood; acids, other
11	constantly filtering our blood on the order of 50	11	toxins, waste products formed by the normal
12	liters a day passing through that filtering	12	metabolism of all the cells in the body. When
13	system. There should be very, very little	13	those waste products build up, they can cause
14	protein coming out. Our body works hard to build	14	illness and if untreated, before we had dialysis,
15	that protein. We want to keep it in. It's one	15	· · · · · · · · · · · · · · · · · · ·
16	of the ways that physicians detect diabetic	16	Q. And you note there early damage shows in
17	kidney damage by testing the urine for protein.	17	blood and urine tests; is that correct?
18	Q. Can I interrupt for a second. The body	18	A. Yeah, current recommendations for the
19	needs those proteins and that's the problem with	19	care of people with diabetes include frequent
20	them leaking through?	20	blood and urine testing. Some of that is to
21	8 8 8	0.4	about the sugar but some of that is also to about
	A. Yes. For example, one of the proteins	21	check the sugar but some of that is also to check
22	A. Yes. For example, one of the proteins is albumin, one of the most common proteins in	22	on the kidney. We can in the urine we can
23	A. Yes. For example, one of the proteins is albumin, one of the most common proteins in the body, forms the white in egg whites. That's	22 23	on the kidney. We can in the urine we can measure the leakiness of the kidney, how much
	A. Yes. For example, one of the proteins is albumin, one of the most common proteins in the body, forms the white in egg whites. That's the protein that gives us allows the	22	on the kidney. We can in the urine we can

	Page 94		Page 96
1	measure a substance called creatinine, a waste	1	MR. SUGGS: Did I do that or did
2	product formed by muscle. When it's normally	2	you?
3	filtered the level should be low in the blood.	3	A SPEAKER: You did it.
4	And as the filtering system of the kidney begins	4	Q. (BY MR. SUGGS) Very good. Can you
5	to deteriorate, we'll start to see levels of this	5	explain to us what's involved in diabetic
6	molecule go up. It's not dangerous in itself but	6	neuropathy?
7	it stands for the collection of other waste	7	A. Sure. Neuropathy is damage to the
8	products that signal trouble.	8	nerves, and as I mentioned a moment ago, that
9	Q. Okay. I think we had another slide here	9	occurs most commonly in the feet and the legs,
10	that further discusses this but I think you may	10	primarily because those nerve cells are
11	have covered some of the items in there. Let me	11	longest longest ones in the body. Most
12	see if I can pull it up. Okay. Did I do that or	12	vulnerable. And when there's damage to the
13	did you do that?	13	vessels that provide nutrition to those small
14	Okay. Could you tell us what's	14	nerves, you get a variety of different problems.
15	involved in this slide, what the later problems	15	You can get paresthesias, this is numbness and
16	are?	16	tingling, pins and needles feeling or you can get
17	A. Sure. Well, early on, kidney disease is	17	chronic pain, shingles-like pain in the leg.
18	pretty asymptomatic. People don't know that they	18	By the same token there can be
19	have it and that's why physicians have to check	19	numbness or even complete loss of sensation, a
20	the urine and the blood to get early signs. You	20	circumstance where someone could step on a tack
21	wouldn't know you have it at all. One of the	21	or a nail and not know it. That creates a big
22	reasons we have two kidneys; there's a bit of	22	risk of undetected injury and in fact, one of the
23	redundancy there. You can take out a whole	23	directions we give to patients with severe
24	kidney. You could lose half your kidney function	24	1 5 5
25	and not notice it. That's the basis for kidney	25	tell you what's happening with a foot. Make sure
	Page 95		Page 97
	5		Page 97
1	transplants. But as kidney function continues to	1	every night before you go to bed you look at the
1 2	transplants. But as kidney function continues to decline, and we go under 50 percent function,	1 2	every night before you go to bed you look at the bottom of your foot. If you can't get your leg
2 3	transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems	1 2 3	every night before you go to bed you look at the bottom of your foot. If you can't get your leg up high enough, use a mirror, and if you still
2	transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems are more serious than just abnormalities on	4	every night before you go to bed you look at the bottom of your foot. If you can't get your leg up high enough, use a mirror, and if you still can't see, have someone else in the family look
2 3 4 5	transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems are more serious than just abnormalities on tests. Now fluid begins to accumulate in the	4 5	every night before you go to bed you look at the bottom of your foot. If you can't get your leg up high enough, use a mirror, and if you still can't see, have someone else in the family look at the bottom of your feet and make sure there's
2 3 4	transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems are more serious than just abnormalities on tests. Now fluid begins to accumulate in the legs and chest, as I mentioned a moment ago.	4 5 6	every night before you go to bed you look at the bottom of your foot. If you can't get your leg up high enough, use a mirror, and if you still can't see, have someone else in the family look at the bottom of your feet and make sure there's not something sticking in it or some infection
2 3 4 5 6 7	transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems are more serious than just abnormalities on tests. Now fluid begins to accumulate in the legs and chest, as I mentioned a moment ago. People don't feel right. Fatigue, loss of	4 5 6 7	every night before you go to bed you look at the bottom of your foot. If you can't get your leg up high enough, use a mirror, and if you still can't see, have someone else in the family look at the bottom of your feet and make sure there's not something sticking in it or some infection there. You get an increased risk of infection.
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	5		5
1	A. Yes, we do. This is an example of what	1	chronic in the smokers than the nonsmokers, then
2	can happen in the foot of someone with diabetes	2	we say chronic bronchitis is associated with
3	where they've lost sensation, and they can't	3	smoking.
4	sense that these things are going on. So, in	4	Q. Does association necessarily means
5	most of us we'd have a callous or an abrasion,	5	causation?
6	we'd pick it up right away. We'd ease up on the	6	A. Causation means when you know that A
7	foot; we'd put a Band-Aid on it; we'd change	7	leads directly to B, or A is an important
8	shoes. They can have pretty serious damage and	8	contributing factor to B, but often A and B can
9	not notice it and it can progress from this kind	9	go together for reasons other than causation.
10	of ulceration to this kind of ulceration, down	10	For example, gray hair predicts the
11	deep penetrating down to the bones underneath.	11	risk of heart disease and stroke. It does
12	When this happens, this is often a sign that not	12	because it's associated with age, but there's an
13	only the superficial skin been infected, but the	13	unmistakeable connection there. My kids when
14	deep parts of the skin and even the bone	14	they were little understood that and used to try
15	underneath.	15	to scrub the gray out of my beard because they
16	MR. SUGGS: Very good. Your Honor,	16	thought that would protect me against getting ill
17	I don't know what time you usually take your	17	the way they saw their grandparents were ill.
18	break.	18	That's a mistake. They saw that gray hair was
19	THE COURT: This would be about it	19	associated with illness, but it's a noncausal
20	if it's a convenient time to break.	20	relationship. It's explained by other factors.
21	MR. SUGGS: This would be a perfect	21	Q. The field of epidemiology, do you use a
22	time. We're about ready to switch gears here.	22	term called risk factor?
23	THE COURT: Ladies and gentlemen of	23	A. Yeah.
24	the jury, we're going to take our first morning	24	Q. What do you mean by that?
25	break. It will be about 15 minutes. Again, I'll	25	A. Commonly know the term risk factor is
	Page 99		Page 101
1	remind you, please don't discuss this case among	1	used a lot, for example, in cardiovascular
2	yourselves or let anyone discuss it with you.	2	disease where we can tick off risk factors for
3	Please try to keep an open mind until you hear	3	heart attack. For example, high blood pressure
4	all the evidence in this case.	4	is a risk factor for heart attack. High
5	We'll be in recess for about 15	5	cholesterol is a risk factor for heart attack.
6	minutes.	6	The interpretation in that setting is that this
7	(Break.)		is a factor that contributes to the occurrence of
8	THE COURT: And we're back on the		the disease and the implication is if we can
9	record and all members of the jury are present.	9	modify that risk factor, if we can change it, if
10	Mr. Suggs.	10	we can reduce it, then we might be able to
11	Q. (BY MR. SUGGS) Thank you, Your Honor.	11	prevent the complication. So, high blood
12	Dr. Brancati, I want to shift gears now and talk	12	pressure is a risk factor for heart disease.
13	about what epidemiologists do to determine what	13	That's been pretty well proven for now in 30
14	factors are associated with the development of	14	years of research and it turns that out if one
15	diabetes. In the field of epidemiology what is	15	reduces blood pressure by treating it with drugs,
16	the definition of the term association?	16	one can help prevent a heart attack.
17	A. We say A is associated with B when they	17	So it's a term we use in
18	go together in studies of patterns of disease and	18	epidemiology when we're identifying a potential
19	population. So, for example, we might say	19	culprit for the occurrence of subsequent disease.
20	cigarette smoking is associated with chronic	20	We do a variety of studies to first see that
21	bronchitis, because if we do a survey and ask	21	association and then as that association grows
22	people about how much they smoke and we also ask	22	stronger and stronger, that relationship may grow
23	them whether or not they have a chronic cough or	23	into a risk factor relationship and get to the
24	they are told by a physician they have chronic	24	point where we say, gee, we know enough about it
25	bronchitis, and we see that bronchitis is more	25	that this is a risk factor we can act on. We

	Page 102		Page 104
1	should go after that risk factor as a means to	1	often true that in epidemiology, we often a
2	prevent its health consequences.	2	lot of our investigative battle is to get
3	Q. When epidemiologists use the term risk	3	relationships from the point of just a vague
4	factor, does that imply that there is some sort	4	association to the point that we say, yeah, this
5	of causal relationship?	5	is looking like a risk factor, we have enough
6	A. Yeah. I'll say that some of my	6	information to act on, either at the clinical
7	colleagues disagree about the precise terminology	7	level in the office or at the public health level
8	because there's no authority that governs the	8	in terms of policy.
9	language specifically, but I'll tell you what I	9	So there are some answers that we
10	do and what we commonly do at Johns Hopkins is	10	never get to 100 percent certainty, and that's so
11	that I use the term risk factor when I'm	11	often true that in epidemiology, we often a
12	thinking that the relationship is probably	12	lot of our investigative battle is to get
13	causal. I say probably because it's often	13	relationships from the point of just a vague
14	impossible to prove with 100 percent certainty a	14	association to the point that we say, yeah, this
15	causal relationship.		is looking like a risk factor, we have enough
16	Take the circumstance with		information to act on, either at the clinical
17 18	cigarette smoking and lung cancer. We have	17	level in the office or at the public health level
19	incredibly strong evidence that cigarette smoking	18 19	in terms of policy.
20	leads to lung cancer, but no one has ever done the definitive experiment to prove it with 100	20	Q. And when epidemiologists say that some factor, whether it's a drug or chemical agent or
21	percent certainty. That experiment would be to	21	whatever increases the risk of developing a
22	take thousands of people at risk for lung cancer	22	disease, does that imply also that there is a
23	who don't smoke, flip a coin, randomly assign		causal relationship?
	some of those folks in that group to smoking,	24	A. Yeah, it implies that we're definitely
25	others in that group to nonsmoking and then	25	thinking there's a causal relationship. Now, for
	Page 103		Page 105
1	continue that for 10, 20, 30 years and count up	1	example, I wouldn't say that gray hair increases
2	the number of lung cancers in each group. Can't	2	the risk of heart attack. I'd say gray hair is a
3	do that. It's not ethical because there's no	3	predictor. But when I use the same increases the
4	presumed health benefit to smoking; it's a		
	1 07	4	
5	harmful exposure. So you could never do that	4 5	risk of it, yeah, I'm thinking it's potentially
	harmful exposure. So you could never do that kind of randomized control trial. You'd never		risk of it, yeah, I'm thinking it's potentially causal. It could always be proved otherwise in a
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1 assigning people to smoking or not but asking1 association. When we say strength in2 people whether they smoked, how much they smoked,2 epidemiology, we mean what's the answer to th3 and then looking at patterns of disease. In that2 epidemiology, we mean what's the answer to th4 setting it was necessary to pool the wisdom of4 with A to get B. Or in this case, using the5 epidemiologists working on that problem and5 example of cigarette smoking, how many more	
3 and then looking at patterns of disease. In that3 question of how many times more likely is som4 setting it was necessary to pool the wisdom of4 with A to get B. Or in this case, using the	
4 setting it was necessary to pool the wisdom of 4 with A to get B. Or in this case, using the	eone
5 epidemiologists working on that problem and 5 example of cigarette smoking, how many more	
	times
6 develop a set of criteria that could be used to 6 likely is a smoker than a nonsmoker to get a	
7 sort out associations without any likely causal 7 specific complication?	
8 link from risk factor associations where it 8 The stronger the more the	
9 looked increasingly likely that there was a 9 greater the number of times or the stronger the	
10 causal connection.10 relationship, the more likely the relationship is	
11In that setting it was necessary to11to be causal. So I gave some examples here, th	e
12 pool the wisdom of epidemiologists working on 12 relationship between smoking and lung cancer,	
13that problem and develop a set of criteria that13extraordinarily extraordinarily strong,	
14 could be used to sort out associations without14 tenfold risk or higher.	
15 any likely causal link from risk factor15Now, there are nonsmokers who get	
16 associations where it looked increasingly likely 16 lung cancer and there are plenty of people who	
17 that there was a causal connection.17 smoke who never get lung cancer. So it's not a	
18Q. And were these criteria that were18lock and key kind of thing. But but in	
19developed, were they called the Bradford Hill19looking at patterns of disease in population, the	
20 criteria?20 odds are stacked against you if you're a smoker	
21A. Yes, Bradford and Hill were two21in terms of lung cancer risk. It's a very strong	
22 epidemiologists working in the field at that22 relationship.	
23 time. And they put forward these criteria and we23Now, not all relationships we look	
24 still use them today. When I quiz Ph.D. students 24 at in epidemiology are that strong. That's among	g
25 at the Johns Hopkins School of Public Health one25 the strongest. In the United States where we	
Page 107 Page	e 109
1 of the common questions we ask is: Can you go 1 enjoy relatively good health at the individual	
2 through the criteria for causality and apply that 2 level and at the public health level, we're often	
3 to their doctoral thesis to make sure that they 3 more concerned with more moderate levels of ris	κ.
4 understand this kind of bedrock concept. 4 For example, I put a more moderate level of	
5 Q. And are these Bradford Hill criteria 5 association here that we're also concerned with	
6 ways of sort of looking at or analyzing the 6 is, for example, the relationship between	
7 evidence that's already there for the purpose of 7 cigarette smoking and heart disease. Compared t)
8 determining whether there's a causal 8 nonsmokers, cigarette smokers are about 50	
9 relationship? 9 percent or 1.5 times more likely to get heart	
10A. Yes. Can be used to sift through10attacks than nonsmokers.	
11 existing evidence so to determine just how 11 It's nowhere near the level of	
12 strong the evidence is and it also helps to12 association the strength of association	
13 helps us to see where the holes are and what the 13 between cigarette smoking and lung cancer but	
14 next bit of research might be to plug a hole. 14 it's still important. It was still one of the	
15 Q. And pull up here on the screen a chart 15 rationales for launching a public health campaign	
16 that you prepared entitled Bradford Hill Criteria 16 to prevent kids from starting smoking, and get	
17 for Causality. Can you walk us through the 17 adults who do smoking to stop smoking. Not onl	у
18 different criteria and explain how they were 18 because would it prevent lung cancer, it would	
19 how those criteria were used in the context of 19 prevent heart disease. And in fact, heart	
20 cigarette smoking where they were originally 20 disease is a lot more common than lung cancer.	
21 developed so that we can understand what these 21 So sometimes as an epidemiologist we're more	
22 criteria are and how epidemiologists use them to 22 interested in the moderate relationships if	
23 determine whether there's a causal relationship? 23 the outcome is a common one. There could be m	ore
24A.Sure. I'd be delighted.24at stake More cases of disease to prevent for the	
25 So one criterion is the strength of 25 more common outcome than the less common out	come.

	Page 110		Page 112
1	Q. The next factor you have there is	1	strongest associations I ever found in a study
2	consistency. What do you mean by that?	2	was the relationship between doughnut consumption
3	A. Consistency has to do with how well	3	and diabetes. And this was early in my career.
4	we're able to replicate the results in different	4	I was dying to publish it. It was highly
5	studies. One one gripe I always have here	5	significant and very strong. It turned out that
6	about epidemiology studies is every morning you	6	people who had diabetes were much less likely to
7	open the paper, heart is bad, coffee is good; it	7	consume doughnuts, and so it actually looked like
8	prevents diabetes. It's bad we go back and	8	doughnuts were protective. As you went from one
9	forth and the epidemiologists argue about it and	9	doughnut to two doughnuts to three doughnuts a
10	creates confusion for public health officials.	10	week, the prevalence of diabetes went
11	There are many circumstances where we get	11	progressively down. So I had a highly
12	consistency done in different parts of the	12	statistically significant result, but I knew it
13	country, done in different countries, different	13	was nonsensical.
14	populations. The more consistent the signal, the	14	In that study we asked about
15	more we say the results are consistent.	15	diabetes and doughnut consumption at the same
16	Q. The next factor you have listed there is	16	point in time, and our interpretation was and
17	specificity. What does that mean?	17	the reason I never submitted it for peer-review
18	A. Specificity has to do with the idea when	18	publication is I assumed, oh, yeah, the people
19	you see A leading to B. It's not also leading to	19	with diabetes, they're eating fewer doughnuts.
20	a whole range of other conditions that really	20	Either their doctor told them to eat fewer
21	don't have anything else to do with B. The	21	doughnuts, or they're eating the doughnuts but
22	reason that's a problem in terms of causality is	22	they're embarrassed to report it, because we're
23	we still have a lot to learn about human biology,	23	asking them about it and they know that they
24	but we know enough that we can connect the dots	24	shouldn't. So in that case we didn't have
25	between different kinds of conditions.	25	temporal sequence between doughnut consumption
	Page 111		5 110
	rage III		Page 113
1	For example, with cigarette	1	and diabetes.
1 2	For example, with cigarette smoking, as experts began to study it, it made	1 2	and diabetes. Now, if we had done that study a
	For example, with cigarette smoking, as experts began to study it, it made sense as the results came in, and it turned out		and diabetes. Now, if we had done that study a little differently and asked about doughnut
2	For example, with cigarette smoking, as experts began to study it, it made sense as the results came in, and it turned out that smoking was a bigger risk factor for cancer	2	and diabetes. Now, if we had done that study a little differently and asked about doughnut consumption and youth and then diabetes in middle
2 3 4 5	For example, with cigarette smoking, as experts began to study it, it made sense as the results came in, and it turned out that smoking was a bigger risk factor for cancer of the lip, the mouth, of the airways, of the	2	and diabetes. Now, if we had done that study a little differently and asked about doughnut consumption and youth and then diabetes in middle age, we would have had that temporal separation.
2 3 4 5	For example, with cigarette smoking, as experts began to study it, it made sense as the results came in, and it turned out that smoking was a bigger risk factor for cancer of the lip, the mouth, of the airways, of the lung, than it was for cancers of the colon or the	2 3 4	and diabetes. Now, if we had done that study a little differently and asked about doughnut consumption and youth and then diabetes in middle age, we would have had that temporal separation. Then we would have known the doughnuts came
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	Page 114		Page 116
1	80 pack years of smoking, someone who has smoked	1	more coherent the whole body of scientific
2	two packs a day for 40 years, they're at much	2	literature, human and nonhuman, the more we're
3	higher risk than someone who's just had 10 pack	3	apt to say, oh, yeah, this looks like a causal
4	years of smoking and quit. So we know that with	4	relationship.
5	cigarette smoking there's a strong biological	5	Q. I think we have two other factors to go
6	gradient or a strong dose response. That also	6	through.
7	adds to the evidence for causality.	7	One is analogy. If I can get it
8	Q. The next factor you have listed is	8	there. Okay. And what does that refer to?
9	plausibility. What does that mean?	9	A. Analogy has to do with what happens when
10	A. Plausibility has to do with how	10	we've already gone down a path. We've already
11	biologically likely the relationship seems. Now,	11	found that that A leads to B, and now we're
12	we don't know everything about human biology,	12	looking at at whether whether Y leads to B.
13	we're still learning. In fact, I'm always	13	And it turns out that A and Y are similar in some
14	surprised when my laboratory colleagues say, we	14	ways, and then we say, oh, that we've we've
15	love it when you epidemiologists come up with	15	sort of already gone down that path, and so I
16	relationships we don't fully understand because	16	know a little bit about this relationship. I'm
17	then we go back to the lab, or we go to our mice	17	not starting from scratch. I'm not starting
18	or our animals and we do studies and try to find	18	flat-footed.
19	out what that means. But we get grief in	19	I that know there's already a
20	epidemiology when we report that A goes with B,	20	relationship between an exposure that's similar
21	but no one was ever thinking about that sort of	21	and the outcome, so that adds to the general
22	association before. Comes out of left field; it	22	evidence. So, for example, researchers did a lot
23	comes out of the blue; it just doesn't seem that	23	of work on cigarette smoking through over a
24	1		period of decades. As time went by, they started
25	So, with smoking and lung cancer,	25	to turn to other elements of tobacco smoke. For
	Page 115		Page 117
1	it was really quite plausible that that kind of	1	example other elements of tobacco, for
1 2		1 2	example other elements of tobacco, for
-	it was really quite plausible that that kind of		example other elements of tobacco, for
2	it was really quite plausible that that kind of damage to the airway could could lead		example other elements of tobacco, for example, chewing tobacco, smoking cigars or most
2 3	it was really quite plausible that that kind of damage to the airway could could lead ultimately to cancer, especially as we learned more about the way the cells of the airway respond to damage from the toxins and cigarette	3	example other elements of tobacco, for example, chewing tobacco, smoking cigars or most recently, passive smoking; all exposures related
2 3 4	it was really quite plausible that that kind of damage to the airway could could lead ultimately to cancer, especially as we learned more about the way the cells of the airway respond to damage from the toxins and cigarette smoke, it became more and more plausible.	3	example other elements of tobacco, for example, chewing tobacco, smoking cigars or most recently, passive smoking; all exposures related to cigarette smoking. But the fact that we knew so much about cigarette smoking made it a little easier to connect the dots in relation to
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1	Page 118		Page 120
	conceptualize; it's very hard to do.	1	
2	Sometimes, though, we do have	2	know that they can be used for risk prediction,
3	experimental evidence like that. Often the	2	identifying which group's at highest risk to go
4	experimental evidence ince that. Orien the	4	after the modifiable factors.
5	little more short-term. For example, there was	5	So the nonmodifiable factors for
6	never the prospect of doing that kind of large,	6	type 2 diabetes that are well established, one is
7	long-term study in cigarette smoking because of	7	age. As people get older, they're more and more
8	the ethical concerns, but there were a number of	l g	likely to have type 2 diabetes. Type 2 diabetes
9	short-term studies taking healthy nonsmokers,	9	is unusual in kids and young adults. Can happen.
10	having them smoke for short periods of time in	10	It's happening more in this country, but it's a
11	controlled circumstances, in hospital research	11	
12	units, and then looking at short-term effects on	12	Another factor is race and
13		13	
14^{13}	their lung function, for example. Those those sorts of experiments		ethnicity. It turns out in the United States that people of European ancestry, we get a
15	could be done and they added to the body of of	15	lot of diabetes, but we get a lot less than
16	evidence. In other circumstances, it's possible	16	people of every other ethnic group in the United
17	to do when it's impossible to do a study that	17	States. So, African-Americans are at higher
18	1		risk, Hispanic Americans are at higher risk,
19	lasts 10 or 20 years, it might be quite feasible to do a study that lasts six or 12 months. In		Native Americans, Pacific Islanders, Native
20	those cases one might not be able to count on		Alaskans, all of those other ethnic groups are at
21	having the complication itself, the event itself,		higher risk than their European counterparts.
22	for example, lung cancer or serious emphysema	22	The third there is family history.
23			I think that's something we all know, that
23	leading to death, but one could find upstream	23	0
24	abnormalities that are on the pathway to the complication.	24	
25	*	25	diabetes. It's always one of the questions we
	Page 119		Page 121
	For example, they might not have	1	
1		_	ask that I ask when someone comes in and
2	full-blown emphysema that restricts them to bed	2	they're concerned about getting diabetes. I know
	full-blown emphysema that restricts them to bed and oxygen, but they might have chronic	1 2 3	they're concerned about getting diabetes. I know their age, their race, ethnicity. I also ask
2	full-blown emphysema that restricts them to bed and oxygen, but they might have chronic bronchitis which is on the way to developing	2	they're concerned about getting diabetes. I know their age, their race, ethnicity. I also ask them about a history of diabetes in the family.
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	 full-blown emphysema that restricts them to bed and oxygen, but they might have chronic bronchitis which is on the way to developing full-blown emphysema. You could test that in the short-term experiment and that would add to the experimental that would add to the evidence base in favor of causality. Q. Dr. Brancati, regarding diabetes, in particular, and leaving aside for a moment the question of whether Zyprexa is involved in diabetes, are there risk factors for diabetes that are well established and accepted in the field of medicine? A. Yes, there are. Q. And let me pull up this next slide, Risk Factors for Type 2 Diabetes. Can you very briefly describe for us the risk factors that are on this slide? A. Sure. I've grouped them into two categories modifiable and nonmodifiable. It's just the jargon we use to mean the factors we can do something about; the factors we can change or 	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	 they're concerned about getting diabetes. I know their age, their race, ethnicity. I also ask them about a history of diabetes in the family. If there's been a lot of it, I worry that they're at high risk. Q And then over on the right-hand side you have the modifiable risk factors. Am I correct that those are the ones that can be altered by behavioral changes to some extent? A. That's correct. These are the ones we have a shot at doing something about. So obesity is the single strongest risk factor for type 2 diabetes. The gradient of risk across the full range of obesity, from lean all the way up to morbidly obese, is well over tenfold. So it's like over the full range of the relationship between cigarette smoking and lung cancer. It is the single biggest risk factor. That's why it's been the target in studies aimed at preventing diabetes and preventing diabetic complications. Q. Dr. Brancati, how much weight gain does it take to significantly increase the risk of
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 9 20 21 22 23	 full-blown emphysema that restricts them to bed and oxygen, but they might have chronic bronchitis which is on the way to developing full-blown emphysema. You could test that in the short-term experiment and that would add to the experimental that would add to the evidence base in favor of causality. Q. Dr. Brancati, regarding diabetes, in particular, and leaving aside for a moment the question of whether Zyprexa is involved in diabetes, are there risk factors for diabetes that are well established and accepted in the field of medicine? A. Yes, there are. Q. And let me pull up this next slide, Risk Factors for Type 2 Diabetes. Can you very briefly describe for us the risk factors that are on this slide? A. Sure. I've grouped them into two categories modifiable and nonmodifiable. It's just the jargon we use to mean the factors we can 	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	 they're concerned about getting diabetes. I know their age, their race, ethnicity. I also ask them about a history of diabetes in the family. If there's been a lot of it, I worry that they're at high risk. Q And then over on the right-hand side you have the modifiable risk factors. Am I correct that those are the ones that can be altered by behavioral changes to some extent? A. That's correct. These are the ones we have a shot at doing something about. So obesity is the single strongest risk factor for type 2 diabetes. The gradient of risk across the full range of obesity, from lean all the way up to morbidly obese, is well over tenfold. So it's like over the full range of the relationship between cigarette smoking and lung cancer. It is the single biggest risk factor. That's why it's been the target in studies aimed at preventing diabetes and preventing diabetic complications. Q. Dr. Brancati, how much weight gain does

	Page 122		Page 124
1	exactly where you're starting, so I'll answer	1	was obese down essentially to their lean weight.
2	that in two ways. In epidemiologic studies that	2	And a lot of Americans are 20, 30, 40 pounds
3	relate that relate degree of obesity to	3	overweight. The story that has developed over
4	subsequent risk of diabetes, the risk	4	the past ten years is that even smaller amounts
5	relationship is exponential, kind of curved	5	of weight loss, bringing someone down only
6	upward, like standing at the base of a mountain	6	partway to their lean weight, could still have
7	and looking up.	7	big benefits. By the same token, weight gains in
8	In judging how much what a bit	8	that range could have major harm. Small
9	of extra weight does is a bit like taking a	9	differences in weight could have a multiplier
10	yardstick and laying it down on that upward	10	effect in terms of diabetes risk.
11	sloping curve. If you're down at the base and	11	Q. I believe you said in response to my
12	you're kind of on very flat ground and you lay	12	prior question one of my prior questions
13	that yardstick down, it won't make much of a	13	that if you took a group of people who tended to
14	difference. You're not going to go up very much	14	be on the heavier side anyway, such as people
15	for going across the yard. But as you get closer	15	with severe mental disorders, and they had an
16	to the base of the mountain or as the weight goes	16	increase of 25 pounds, you said that there were
17	up, you lay down that yardstick, it starts	17	some studies that if that weight gain was spread
18	tilting up along the side of the mountain. So	18	out over a decade or so, it could be on the order
19	when you start a little higher, the same amount	19	of a three or four times increase; is that
20	of weight gain at a lower base that wouldn't have	20	correct?
21	posed much risk at all can now pose more	21	A. Yeah. Well
22	substantial risk.	22	Q. Let me follow up with what exactly that
23	Q. Dr. Brancati, are people with severe	23	means.
24	mental disorders, do they have a higher	24	If there's a 3 or 400 pardon
25	prevalence of obesity?	25	me three or four times higher risk for that
	Page 123		Page 125
1	A. They do.	1	group of folks getting diabetes, what does that
2	Q. With people in that category, if a group	2	translate to in terms of percentage?
3	of people had weight gain of 25 pounds in a year,	3	A. Well, threefold higher would be 300
4	what would that do to their increased risk of	4	percent higher.
5	diabetes?	5	Q. And fourfold would be 40 percent?
6	A. If they're starting overweight or obese,	6	A. 400 percent.
7	it could pose a substantial additional risk. In	7	Q. And if the weight gain was occurring not
8	some studies that weight gain, even spread out	8	over with that group was occurring not over
9	over a period of decades, can be associated with	9	decades, but over the course of a year, would
10	a three, or fourfold increase in the risk of	10	that tend to enhance the increased risk or lessen
11	diabetes.	11	it?
12	The other way to look at it is in	12	A. It's a good question. We don't know
13	studies of people who are right on the verge of	13	exactly, but you'd have to figure it's at least
14	getting diabetes and asking them to lose weight.	14	the same degree of risk, at least the same
15	In those studies even weight loss on the order of	15	degree.
16	5 percent. So in someone who weighs 200 pounds,	16	Q. Okay. Let's switch gears and talk about
17	that might be just 10 pounds worth of weight	17	Zyprexa in particular.
18	loss, even that little bit of weight loss has a	18	Are you generally familiar with
19	big effect on lowering the risk of diabetes over	19	that drug?
20	the next four years.	20	A. Yes.
21	So that's been one of the stories,	21	Q. And what is it?
22	I think, in the past ten years in this field is	22	A. It's a second-generation antipsychotic
23	that many of us presume that that the only	23	drug. It was developed to modify chemistry of
24	hope to reduce the risk of diabetes related to	24	the brain and treat people with psychosis, people
25	obesity was to get everyone from everyone who	25	who have severe hallucinations or delusions

Page 126Page1 related to underlying psychiatric disease.1described of collecting the 100 or so scientific2 Q. And do you know whether it was indicateda for the treatment of schizophrenics and the acutea tricles for review, is that how you conduct3 for the treatment of schizophrenics and the acutea tricles for review, is that how you conductthose types of reviews during the normal course4 manic phase of bipolar disorder?5A. Yes, it is.5A. That's exactly right. At Hopkins we6 Q. Are there any peer-reviewed scientific7systematic reviews, where we're charged by the7 articles addressing the issue of whether Zyprexa8and other atypical antipsychotic drugs are99 associated with an increased risk of diabetes?9a particular area in order to write a report that10 A. Yes, very many.110could help physicians or policymakers or insure11 Q. Roughly, how many are there?11set policy, and we use a very similar approach.12 A. I reviewed over 100.12Q. Okay. And how was it that you went14 about collecting those articles for review? Was13you reviewed, when did they first begin to be14 about collecting those articles for review?14ublished in the scientific literature? Let me15 it something that I gave you or any other lawyer16Were these articles that you17 articles?18A. No, not not at all. We got them from1718A. No, not not at all. We got them from18journals that you described earlier?
 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? 2 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? 2 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?
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17 articles? 17 reviewed, were they in the peer-reviewed type of
1 ± 0 A. No, not not at an. We got them from 1 ± 0 journals that you described earlier?
19 a variety of approaches. One thing that we do 19 A. Yes, peer reviewed.
20 very commonly in research is go to the web site 20 Q. Did you restrict yourself to
21 of the National Library of Medicine that allows 21 peer-reviewed articles?
22 us to do very efficient electronic searches. So 22 A. We did, yes.
23 we could put in terms like antipsychotic drugs or 23 Q. And why did you restrict yourself to
24 specific names of drugs and then put in terms for 24 those articles?
25 diabetes, ask the program to match it, and then 25 A. Those are the higher quality papers.
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1 the National Library of Medicine will pull up1 The peer-reviewed papers, as I mentioned a few2 electronic copies of journals. That's how we got2 minutes ago, are the ones that have been subject
3 to most of the papers. 3 to the most scrutiny, candid scrutiny by peers a
4 I also looked at review articles on 4 other institutions. So one of the rules we have
5 the topic and dug back through the bibliographies 5 in academia is when you write a paper, you can
6 in those review articles, and then I took notes 6 almost always get it published somewhere. You
7 at conferences given by medical experts and those 7 just keep sending it around. Even if your peers
8 sorts of things. 8 think the science is bad, you can find someplac
9 Q. You said that that was how "we" got 9 for it because there are plenty of journals out
10
11 assistance in collecting articles for review? 11 I don't like to rely on those
12A.Yeah. Part I did. Part of my12I unit include to rely on those12A.Yeah. Part I did. Part of my12sources when I'm writing a report. We also do
13 approach when I'm asked to draft a report, either 13 like to publish there because my colleagues at
14 this type or other types for the federal 14 Ke to publish there because my conceduces at 14 Hopkins will know that we've taken the low ro
15 government, is for a variety of reasons I ask 15 mistead of the high road, so the gold standard in
16 some of the junior colleagues around me to help. 16 the field is the peer-reviewed scientific
17 First, it gives them some experience. Second, it 17 journals.
18 allows me to deliver a product that's more 18 Q. Okay. Of those 100 or so peer-reviewed
19 complete and and more and more on time. 19 journal articles that you reviewed, when was it
20 And in situations like this, I rely on people to 20 that they first began to be published with
21 pull articles for me, abstract information, do 21 respect to linking Zyprexa with diabetes?
22 some initial drafting, and then I look at it and 22 A. Well, really from the you know, mid
23 make sure it reflects my views before I present 23 to late '90s and then through the end of 2006
24 it to the outside world. 24 when I wrote the report.
25 Q. And is this process that you've 25 Q. Okay. And I'd like to talk about the

	Page 130		Page 132
1	different types of scientific evidence.	1	going on here. I really didn't expect it the
2	Let me ask you this question:	2	first time. Now I've seen three or four cases.
3	These articles that you reviewed, do they for the	3	Now I feel motivated enough to write it up.
4	most part report on various types of studies that	4	Q. And can a peer case report just standing
5	were done to analyze the question of whether	5	alone ever prove causation?
6	Zyprexa is related with hyperglycemia or	6	A. No, it can't. Really, no one study by
7	diabetes?	7	itself, with the exception of that hypothetical
8	A. Yes.	8	long-term, randomized human experiment, ever
9	Q. Okay. And I presume there were also	9	nails causality. Case reports and case series
10	some review articles that reviewed the literature	10	more so than most, because they're anecdotal,
11	as well?		they're single episodes. But having said that,
12	A. Yes.		it's an important part of the scientific
13	Q. With respect to those articles that		literature, because often we never get to the
14	talked about studies that were conducted, would	14	other studies unless there's some suspicion based
15	it be fair to say that there were probably	15	1 2
16	several different types of methodologies that can		there are elements of those studies that can add
17	be used to conduct such studies?		to their persuasiveness depending on the nature
18	A. Yes.	18	of the case report.
19	Q. Okay. And do we have a chart here that	19	Q. Are those case report well, let me
20	just sort of lists the different types of studies	20	ask this: Are there particular types of case
21	that were done to address the question of whether	21	reports that can, indeed, provide evidence of
22	Zyprexa is related to diabetes?		causality?
23	A. Yes.	23	A. The type of case report or case series
24	Q. There we go. Sometimes it works,	24	
25	sometimes it doesn't.	25	relationship are the ones where there's been a
	Page 131		Page 133
1	This chart's entitled, Types of	1	dechallenge and/or a rechallenge. What do I mean
2	Scientific Evidence Available to Determine	2	by that? The pharmacologists, my colleagues in
3	Whether Zyprexa Causes Diabetes, and then we have	3	that field, people who study drugs for a living,
4	listed there five different types of of	4	they'll consider the initial use of a drug to be
5	studies that were available in this area; is that		the challenge. Somebody goes on drug X and then
6	correct?	6	they get sick and that's the initial challenge.
7	A. That's right.	7	Now, the dechallenge is when the
8	Q. Okay. And can you just briefly describe	8	drug is withdrawn. So, you give someone a new
9	for us what type of what's involved in a case	9	drug, they develop wheezing and asthma. You take
10	report or a case series?	10	them off the drug. If the wheezing and asthma
11	A. A case report is very much what it	11	continues, you say, well, maybe it was the drug
12	sounds like. It's a case that sparked the	12	that started it, but, gee, I wonder why they
13	curiosity or suspicion of an individual physician	13	still have it now.
14	about an individual patient. They saw something	14	You get dechallenge evidence of an
15	going on with that event that they thought other	15	association when they felt fine; you give the
16	doctors should know about and they write up that	16	drug; they get wheezing and asthma; you take the
17	case.	17	drug off; wheezing and asthma gets better. Now
18 19	Q. Okay.	18	it looks like, gee, maybe it wasn't the drug,
19	A. The case series is a series of those	19	because they didn't have it before; they don't
20 21	kinds of cases. So, maybe when they saw the first case, they were a little suspicious, but	20 21	have it now; it was only when they were on the
21	they weren't really moved to write anything up,	21	drug. Now, if you really want even
23	to take the time to do it. But when they saw the	23	greater proof and the physician and the patient
24	second or the third or the fourth case, they say	24	are willing, you can try a rechallenge. So they
24	to themselves, hey, I think there's something	24	felt fine; put them on the drug, wheezing and
20	to memberves, ney, I units there s something	23	ion me, put mem on me urug, wheezing and

	Page 134		Page 136
1	asthma; take them off the drug, wheezing and	1	A. There were cohort studies as well. The
2	asthma goes away. Then the physician and the	2	term comes from actually Roman history. Cohorts
3	patient say, you know, I'd really like that drug.	3	in the Roman legion Roman warriors were formed
4	It was really helping me in other ways. Are we	4	into cohorts, groups of about 4- to 500 men who
5	100 percent certain that it was the drug? You	5	were led by a commander, and the legions would
6	say, okay, let's try a rechallenge. So, start	6	form them up in order to keep track of the troops
7	the drug again. If wheezing and asthma comes	7	and be able to do head counts at the end of the
8	back, you say, gee, it seems like it's got to be	8	day. So you'd send a cohort into battle, you
9	the drug. What else could explain that kind of	9	know exactly how many were there. At the end of
10	pattern?	10	the day you'd count heads and you'd see where
11	Q. The next type of study is what you call	11	your losses were in what field of battle, and
12	cross-sectional studies. Were there	12	•
13	cross-sectional studies relating to this issue of	13	next day.
14	whether Zyprexa causes diabetes?	14	In epidemiologic studies, cohort
15	A. There were.	15	studies are similar. You form a group of people;
16	Q. What's involved in that type of study?	16	you account for every head. Instead of sending
17	A. A cross-sectional study is like the	17	them into battle with ancient armies, you send
18	study of the doughnuts and diabetes I mentioned a	18	them to do battle with the forces of disease and
19	little while ago. Those studies are where you	19	you count heads if you're looking at mortality or
20	take a group of people and you survey them and	20	you count cases of disease according to their
21	you see, do they have diabetes now? Are they	21	risk factor status of baseline and then make
22	eating doughnuts now? Do they have diabetes now?	22	judgments about risk on that basis.
23	Are they taking Zyprexa now?	23	Q. And, finally, it appears that there were
24	It's not the optimal study designed	24	experimental studies that were also available to
25	for making inferences about causal relationships		look at this issue whether Zyprexa causes
	Page 135		Page 137
1			
L 1	for the reason that I mentioned to you before.	1	diabetes?
1 2	for the reason that I mentioned to you before. You don't know what they were taking before. You	1 2	diabetes? A. Yes, there were, Experimental studies
2	You don't know what they were taking before. You	2	A. Yes, there were. Experimental studies
2 3	You don't know what they were taking before. You don't know how they ended up on the drug now.		A. Yes, there were. Experimental studies were of the type I mentioned before where you
2 3 4	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went	2 3 4	A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or
2 3	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a	2 3 4 5	A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to
2 3 4 5	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker	2 3 4	A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or
2 3 4 5 6	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker designs.	2 3 4 5 6	A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road.
2 3 4 5 6 7	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker	2 3 4 5 6 7	A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road.Q. Okay. Let's take a look at what the
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2 3 4 5 6 7 8 9	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker designs. Q. Were there case-control studies addressing the issue of whether Zyprexa can cause	2 3 4 5 6 7 8 9	A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road.Q. Okay. Let's take a look at what the results were of your analyses with respect to each of these different categories or types of
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker designs. Q. Were there case-control studies addressing the issue of whether Zyprexa can cause diabetes? A. There were. The idea behind a case-control study is that you try to arrive at some temporal sequence. For example, in the diabetes and doughnut example, rather than asking them, how many doughnuts are you eating now, you group people into diabetic or nondiabetic. Then you ask them, how many doughnuts did you used to eat five years ago or ten years ago. Pick a point in time before they would have developed the disease, and then make judgments about the relationship between the risk factor and the	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	 A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road. Q. Okay. Let's take a look at what the results were of your analyses with respect to each of these different categories or types of evidence. Let's first talk about what the case reports and the case series say with respect to Zyprexa and diabetes. I think we've got a table here pardon me a slide here that summarizes that. There we go. Can you describe for us what you found with respect to the case reports regarding the connection between Zyprexa and diabetes? A. Well, we found many case reports of diabetes occurring in people who use Zyprexa, or
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker designs. Q. Were there case-control studies addressing the issue of whether Zyprexa can cause diabetes? A. There were. The idea behind a case-control study is that you try to arrive at some temporal sequence. For example, in the diabetes and doughnut example, rather than asking them, how many doughnuts are you eating now, you group people into diabetic or nondiabetic. Then you ask them, how many doughnuts did you used to eat five years ago or ten years ago. Pick a point in time before they would have developed the disease, and then make judgments about the relationship between the risk factor and the outcome.	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	 A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road. Q. Okay. Let's take a look at what the results were of your analyses with respect to each of these different categories or types of evidence. Let's first talk about what the case reports and the case series say with respect to Zyprexa and diabetes. I think we've got a table here pardon me a slide here that summarizes that. There we go. Can you describe for us what you found with respect to the case reports regarding the connection between Zyprexa and diabetes? A. Well, we found many case reports of diabetes who went
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	You don't know what they were taking before. You don't know how they ended up on the drug now. Maybe they were taken the drug before and went off because they had symptoms. It's hard a little hard to tell. It's one of the weaker designs. Q. Were there case-control studies addressing the issue of whether Zyprexa can cause diabetes? A. There were. The idea behind a case-control study is that you try to arrive at some temporal sequence. For example, in the diabetes and doughnut example, rather than asking them, how many doughnuts are you eating now, you group people into diabetic or nondiabetic. Then you ask them, how many doughnuts did you used to eat five years ago or ten years ago. Pick a point in time before they would have developed the disease, and then make judgments about the relationship between the risk factor and the outcome.	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	 A. Yes, there were. Experimental studies were of the type I mentioned before where you take groups of people without the disease or condition of interest, randomly assign them to drug or no drug, and then see what happens down the road. Q. Okay. Let's take a look at what the results were of your analyses with respect to each of these different categories or types of evidence. Let's first talk about what the case reports and the case series say with respect to Zyprexa and diabetes. I think we've got a table here pardon me a slide here that summarizes that. There we go. Can you describe for us what you found with respect to the case reports regarding the connection between Zyprexa and diabetes? A. Well, we found many case reports of diabetes who went

	Page 138		Page 140
1	in the normal range or the diabetic range. There	1	the study, not an optimal scientific design. So
2	was a good bit of dechallenge evidence.	2	I think we found a few of them because colleagues
3	And one of the FDA reports reported	3	who were studying this decided to do a few of
4	ten cases ten cases where there was a	4	them decided on other designs that would be
5	dechallenge and a rechallenge, and in most of	5	stronger.
6	those and in most of those cases the	б	Q. Okay. And I think the next category of
7	hyperglycemia improved after the Zyprexa was	7	studies you looked at was case-control studies;
8	taken off and got worse again after the Zyprexa	8	is that correct?
9	was added back.	9	A. That's right.
10	Q. And what did you draw from those ten	10	Q. And tell us what you found when you
11	cases?	11	looked at the case-control studies that addressed
12	A. Well, that as I mentioned before, the	12	the issue of whether Zyprexa can cause diabetes
13	dechallenge/rechallenge type of case report,	13	or hyperglycemia.
14	that's that raises my suspicion that there	14	A. These case-control designs involve
15	might be a causal relationship.	15	finding people with diabetes, people without, and
16	Q. Okay. And you also note that the FDA	16	then going back in their records to see who was
17	reports hundreds of cases of hyperglycemia in	17	using Zyprexa, who was using another
18	people using atypical antipsychotic drugs; is	18	antipsychotic drug, who wasn't using any
19	that correct?	19	antipsychotic drug. And if you find more Zyprexa
20	A. That's right.	20	use in the people more prior Zyprexa use in
21	Q. And you were looking at those reports	21	the people with diabetes, the cases, then the
22	not only in connection with Zyprexa, but also	22	people without diabetes, the controls, then you
23 24	other atypical antipsychotics; is that correct?	23	surmise, gee, Zyprexa looks like it was a risk
24 25	A. That's right. In our review we really looked across the whole range of antipsychotic	24 25	factor for developing diabetes. And in four of the five studies we
25		25	
	Page 139		Page 141
1	drugs to put Zyprexa in context.	1	found an increased risk of diabetes in connection
2	Q. And the other drugs you have listed	2	with the use of atypical antipsychotic drugs, and
3	there, clozapine, greater than Zyprexa, greater	3	Zyprexa was one of the leading factors. And in
4	than risperidone, greater than quetiapine; is	4	one study they were able to show a gradient,
5	that correct?	5 6	again with clozapine, the oldest of the atypical
6 7	A. That's right. Most of the case reports		antipsychotics on top. In this case, Zyprexa and
8	pertain to clozapine, but Zyprexa was up there nearby. There was a gradient of risks	8	risperidone second, and then quetiapine, again, down lower than Zyprexa. So, again, a gradient
9	across the different types of atypical	9	of risks across different types of antipsychotic
10	antipsychotic drugs.	10	drugs.
11	Q. Okay. Let's look at what you found with	11	Q. Okay. And I believe you looked at a
12	respect to cross-sectional studies and the link		number of cohort studies pardon me as well;
13	between Zyprexa and diabetes.	13	is that correct?
14	What did you find with respect to	14	A. We did.
15	those studies? First of all, how many were there	15	Q. And I think the slide that we have for
16	and what were the results?	16	that one shows that there were 17 cohort studies;
17	A. We found three cross-sectional studies.	17	is that correct?
18	The results here were mixed. We didn't expect	18	A. Yeah, there were a lot of cohort
19	much and didn't find much.	19	studies. This is a good design for looking at
20	Q. Why didn't you expect much from this	20	risks associated with a drug. The majority of
21	type of study?	21	them found associations between antipsychotic
22	A. For the reasons I mentioned before.	22	drugs and the subsequent risk of diabetes. Some
23	Cross-sectional studies are subject to these	23	of those had to do with atypicals relative to
24	problems of which came first, the chicken or the	24	typical drugs. Some of those had to do with
25	egg. It's not an optimal design, I think, for	25	Zyprexa versus other atypical antipsychotics.

	Page 142		Page 144
1	Some of them had to do with the	1	of evidence where you have a variety of
2	effects of Zyprexa in people with established	2	widely-used drugs in the same trial compared head
3	diabetes. Not all of the cohort studies showed	3	to head. And in CATIE, Zyprexa was associated
4	significant signal, but the majority did. And	4	with weight gain and with increase in blood
5	consistent with the case reports and the cohort	5	glucose measured indirectly through this entity
6	studies, it looked like Zyprexa was among the	6	called hemoglobin A1C.
7	antipsychotic agents most likely to be associated	7	Q. I think we're probably going to be
8	with the subsequent risk of diabetes.	8	hearing more about that term as we go through the
9	Q. And you note in your last point there	9	trial. Can we take a bit of time here and
10	that two studies found increased risk of diabetes	10	explain to the jury just what's involved in that
11	in Zyprexa users over risperidone users; is that		hemoglobin A1C test and how it measures blood
12	correct?	12	glucose?
13	A. Yes.	13	A. Sure. To explain that, let me take you
14	Q. Does that mean the risk was higher for	14	back to the early 1980s when I was in medical
15	Zyprexa users	15	school and I was taught to take care of people
16	A. Than risperidone, yes.		with diabetes. In those days, before we had this
17	1	17	
18	Q. Okay. Were there also some experimental studies that addressed this issue?	18	A1C assay, to determine how someone was doing in terms of their blood sugar level, we had to rely
19	A. There were.	19	on blood tests, venapuncture of the arm and
20	Q. Pulling up the next slide. Can you	20	sending that off to a lab. A little
21	describe the experimental studies and what they	21	uncomfortable, a little cumbersome. Or we'd
22	showed?	22	check the urine with strips and see how much
23	A. Sure. Well, again, keep in mind that	23	glucose was spilling over in the urine.
24	• •	24	These weren't the best tests
25	study comparing all the antipsychotic agents in	25	
2.5		25	
	Page 143		
			Page 145
1	regards to diabetes and other types of related	1	people with diabetes, bringing them back every
1 2		1 2	
	regards to diabetes and other types of related	1 2 3	people with diabetes, bringing them back every two or three months in the office, and then our judgment about their control would be staked on a
2	regards to diabetes and other types of related outcomes like heart disease or so on. So the		people with diabetes, bringing them back every two or three months in the office, and then our
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	Page 146		Page 148
1	that.	1	to let people come whenever they want, 8:00 in
2	That's why the A1C was developed.	2	the morning, 2:00 in the afternoon, 6:00 at
3	This is a test that relies on an interesting and	3	night. It's easier to do that. Many studies
4	incidental biochemical fact, and that is that	4	outside the diabetes and heart disease world do
5	blood sugar tends to bind to the hemoglobin	5	that. They let people come back any time of day.
6	molecule. Hemoglobin may sound vaguely familiar	6	That creates a little bit of a
7	to you. If it does, it's because it's one of the	7	problem when you go back and try to figure out if
8	most common proteins in the body. It's what	8	your medication is causing problems in terms of
9	carries oxygen in blood. Actually the iron in	9	blood sugar, because the blood sugar varies so
10	blood is bound to hemoglobin. That's what gives	10	much during the day you introduce a lot of noise.
11	blood its red color. So there's a lot of it, and	11	That's one of the inherent problems in the
12	it circulated all throughout the body.	12	literature around blood sugar and antipsychotic
13	Now, what does hemoglobin have to	13	drugs. There's a lot of noise introduced by the
14	do with diabetes or sugar? Really, nothing,	14	fact that in many of the studies participants
15	except there's so much of it acts like an	15	came back at different times of day. After a
16	incidental an accidental bystander, actually a	16	meal the blood sugar can be a lot higher.
17	little bit like a sponge and it absorbs a little	17	The CATIE investigator showed a lot
18	bit of blood sugar, and a single sugar molecule	18	of foresight by building in the A1C. They were
19	combined on to one sticky end of a hemoglobin.	19	thinking about the hypothesis that Zyprexa and
20	In people without diabetes, about 5	20	other atypical antipsychotic drugs might provoke
21	percent of all the hemoglobin molecules	21	hyperglycemia. They measured blood sugar, but
22	circulating in the blood have a sugar attached.	22	predictably they got a lot of noise in that
23	We say their hemoglobin A1C is 5 percent. That's	23	measurement. They also built in the A1C so they
24	at normal levels of blood sugar. As the blood	24	can get a precise measurement. We don't have
25	sugar rises, that percentage goes up. It goes	25	this in many studies of hyperglycemia, but in one
	Page 147		Page 149
1	from 5 to 6 percent to 7 percent, can go to 11 or	1	of the best and biggest studies we do.
2	12 percent. Doctors compare notes, the highest	2	And Zyprexa raised hemoglobin A1C
3	A1C they've ever seen. Could be 13 or 14	3	about .4 percent. One percent is about 35
4	percent. Each 1 percentage of A1C represents	4	milligrams per deciliter; .4 percent is around 15
5	about 35 milligrams per deciliter of glucose.	5	or 17 milligrams per deciliter. It turns out it
6	The great thing about A1C and the		
		6	actually jibes pretty well with some of the other
7	reason it's so widely used in practice now is	6	
7 8	that it's really impervious to what happened the		actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result.
-	that it's really impervious to what happened the night before or what happened the morning of the	7 8 9	actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result. Q. Just to make sure I understand this.
8 9 10	that it's really impervious to what happened the night before or what happened the morning of the test or even what happened the week before. It	7 8	actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result. Q. Just to make sure I understand this. The CATIE study which used that
8 9 10 11	that it's really impervious to what happened the night before or what happened the morning of the test or even what happened the week before. It ends up being a time average of blood sugars over	7 8 9 10 11	actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result. Q. Just to make sure I understand this. The CATIE study which used that hemoglobin A1C test found that Zyprexa users had
8 9 10 11 12	that it's really impervious to what happened the night before or what happened the morning of the test or even what happened the week before. It ends up being a time average of blood sugars over the life of the red blood cell. Red blood cells	7 8 9 10 11 12	actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result. Q. Just to make sure I understand this. The CATIE study which used that hemoglobin A1C test found that Zyprexa users had higher levels of blood glucose as compared to
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8 9 10 11 12	that it's really impervious to what happened the night before or what happened the morning of the test or even what happened the week before. It ends up being a time average of blood sugars over the life of the red blood cell. Red blood cells circulate for about three months, so this is a biological average of blood sugar over a period	7 8 9 10 11 12 13 14	actually jibes pretty well with some of the other studies that looked at glucose alone. So it ended up being a pretty compelling result. Q. Just to make sure I understand this. The CATIE study which used that hemoglobin A1C test found that Zyprexa users had higher levels of blood glucose as compared to risperidone users and for perphenazine users and ziprasidone; is that correct?
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	Page 150		Page 152
1	blood glucose, often that shows more of a signal	1	Q. (BY MR. SUGGS) Doctor, could you walk
2	than the A1C because it takes persistently high	2	us through the Bradford-Hill criteria in
3	glucoses to budge an A1C. But if it's a good	3	connection with the studies that you've reviewed
4	hedge against the noise in the just the simple	4	and tell us whether the scientific evidence that
5	glucose measurement because it's a nice time	5	you've reviewed satisfies the Bradford-Hill
6	average.	6	criteria and demonstrates that Zyprexa can cause
7	Q. And is the trade name for risperidone	7	diabetes.
8	Risperdal?	8	A. Sure. Well, I think there's pretty good
9	A. Yes.	9	evidence in all of these domains with the
10	Q. Is the trade name for ziprasidone	10	possible exception with the likely exception
11	Geodon?	11	of biological gradient. Let me start at the top
12	A. Yes.	12	and go through the other domains.
13	Q. Do you know the trade name for	13	So, first is strength, and the
14	perphenazine?		relative risks, the degree to which Zyprexa
15	A. I forget offhand.	15	appears to multiply the risk of diabetes. It is
16	Q. I did too. I was hoping you would know.	16	quite variable. It ranges from lows in the 1.5
17 18	We talked earlier about the		to 2 range, all the way up to the 4 or 5-fold
19	Bradford-Hill criteria and how epidemiologists		range depending on the study design. One nice way to settle that would be in experimental
20	use those criteria to evaluate whether a	20	studies, but none of the experimental studies
21	relationship is causal. You've now told us the	21	have been taken all the way out to the occurrence
22	findings or summarized the findings from these	22	of diabetes, so we can quantify the effect on
23	various different types of evidence contained in		blood sugar A1C; we can't really quantify the
24	these different types of studies.		long-term effects on diabetes risk. But I think
25	What I'd like for you to do now for		the strength is in the moderate range.
	Page 151		Page 153
1	us, Doctor, is I'm going to pull back up the	1	Consistency; there's a lot of that
2	Bradford-Hill slide listing those criteria, and	2	
		<u> </u>	in my opinion. I see that same sort of gradient
3	e	∠ 3	in my opinion. I see that same sort of gradient of risk in the case reports, in the include
3 4	I'd like you to tell the jury whether the	2 3 4	of risk in the case reports, in the include the dechallenge and rechallenge component. I see
	e		of risk in the case reports, in the include
4	I'd like you to tell the jury whether the evidence that you've seen, the review of 100	4	of risk in the case reports, in the include the dechallenge and rechallenge component. I see
4 5	I'd like you to tell the jury whether the evidence that you've seen, the review of 100 articles, using the Bradford-Hill criteria	4 5	of risk in the case reports, in the include the dechallenge and rechallenge component. I see the consistency in the case-control studies, the cohort studies, and the experimental studies even though not taken all the way to the occurrence of
4 5 6 7 8	I'd like you to tell the jury whether the evidence that you've seen, the review of 100 articles, using the Bradford-Hill criteria demonstrates causality. Will you do that for us? A Sure.	4 5	of risk in the case reports, in the include the dechallenge and rechallenge component. I see the consistency in the case-control studies, the cohort studies, and the experimental studies even though not taken all the way to the occurrence of diabetes. It's consistent because you see
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	Page 154		Page 156
1	certainly the experimental studies where the	1	that Allison and colleagues in 1999 asked the
2	exposure to Zyprexa was specifically manipulated	2	question of how weight changes in the presence of
3	as part of the science.	3	antipsychotic drug use. They synthesized the
4	Biological gradient, I lead off	4	literature up to that point. They did this
5	saying I didn't really see great evidence there	5	weighted average that I described. The weighted
6	in terms of duration of dose or the amount of	6	average is along the Y axis here. The dot
7	Zyprexa taken, so I think that's a weak spot.	7	represents their best estimate of the pooled
8	Plausibility; I'd say we didn't	8	average weight gain.
9	go after animal studies, but the references we	9	These bars represent something
10	saw in the reviews, I think, were consistent	10	called 95 percent confidence intervals. The
11	enough that the results were biologically	11	bigger the bars, the more blurry the dot, the
12	plausible. And I think the biggest factor here	12	less certain we are of it. But once you go
13	for me was the very strong association between	13	beyond as long as you're within these bars,
14	Zyprexa and substantial weight gain. Weight	14	you're pretty certain you're looking at the
15	gain, as I said a few moments ago, is the leading	15	the statistically accurate effects. So smaller
16	risk factor, the single strongest risk factor for	16	1 2
17	the occurrence of type 2 diabetes.	17	looked at the literature, then they looked at
18	I could believe that a drug could	18	what happened to body weight in people with
19	lead to type 2 diabetes without leading to	19	psychotic disorders
20	obesity, but a drug that leads to obesity, right	20	Q. This was just over ten weeks, correct?
21	off the bat I have to say, oh, this could be a	21	A. Just over ten weeks. What happened to
22	drug where one of the consequences would be	22	body weight over ten weeks according to the
23	increased risk of type 2 diabetes, so it makes	23	different antipsychotic drugs used. Here's
24 25	those relationships quite plausible.	24	Haloperidol. It's an old-fashioned
25	Q. Can I pause there and show another slide	25	first-generation drug. Here's placebo, so it's
	Page 155		Page 157
1	from your report that shows the weight change	1	something that's not effective at all. And,
2	after ten weeks with various drugs and put that	2	again, you know, as we saw before, olanzapine and
3	in the context with this with this issue of	3	clozapine up high here in terms of weight gain,
4	plausibility.	4	and olanzapine up in the range of a 4 kilogram
5	Can you describe for us what this	5	weight gain. A kilo is about 2.2 pounds, so this
6 7	chart shows?		was on the order of eight or nine pounds of
-	A. These are results from a meta analysis	8	weight gain in ten weeks. Ω Is that a large amount of weight gain in
8 9	published in 1999 by Dr. Allison and colleagues. A meta analysis is one of the techniques that we		Q. Is that a large amount of weight gain in
10			that short a period of time in your opinion?
	• •	9	that short a period of time in your opinion?
	use when we're doing a very systematic rigorous	10	A. Sure. That's a lot to gain in a short
11	use when we're doing a very systematic rigorous review of the published literature where we not		A. Sure. That's a lot to gain in a short period, because if you play that out over a year,
11 12	use when we're doing a very systematic rigorous review of the published literature where we not only sift through the literature and form an	10 11 12	A. Sure. That's a lot to gain in a short period, because if you play that out over a year, five times that, 40 pounds in a year. That's a
11 12 13	use when we're doing a very systematic rigorous review of the published literature where we not only sift through the literature and form an opinion, but we actually go through the data in	10 11 12 13	A. Sure. That's a lot to gain in a short period, because if you play that out over a year, five times that, 40 pounds in a year. That's a lot.
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	Page 158		Page 160
1	in my opinion that we we already knew it was a	1	leading questions. I just raise that as an
2	strong risk factor for weight gain. Weight gain	2	objection.
3	is the leading risk factor for type 2 diabetes,	3	THE COURT: He's an expert witness
4	so one can connect the dots.	4	and I generally allow a certain amount of
5	Q. Let me go back to the Bradford-Hill	5	latitude with that. Mr. Suggs, if you could keep
6	table, because there were a couple of other	6	it down to more of a minimum, but I'll give him
7	criteria there that you haven't addressed yet	7	some latitude with an expert witness as I will
8	with respect to these studies that were targeted,	8	Lilly.
9	looking at the relationship of Zyprexa and	9	MR. KANTRA: Sure. Thank you, sir.
10	diabetes. I think we left off with plausibility.	10	Q. (BY MR. SUGGS) Dr. Brancati, with
11	Can you tell us whether those	11	respect to the chemical properties or the
12	studies that you looked at also met the criteria	12	molecular properties of a drug, what significance
13	of coherence?	13	do you see when when different drugs with
14	A. Yeah, I think the literature in this	14	similar chemical properties or similar chemical
15	field is pretty coherent. It's not only the full	15	structures, what strike that. Let me start
16	range of human studies that I mentioned, but also	16	over.
17	congruence with data from animal studies, animals	17	What's the significance of similar
18	exposed to Zyprexa that gain weight and develop	18	chemical properties, Dr. Brancati?
19	similar metabolic disorders. The sense in the	19	A. Well, you know, as I said before, I'm
20	field is that there's pretty coherent evidence	20	not a pharmacologist or an organic chemist, but
21	across the board.	21	my understanding was that from reviewing this
22	Q. And how about the issue or the	22	literature is Lilly made a great advance in
23	criteria, rather, of analogy? Does the data fit		developing olanzapine or Zyprexa, because
24	and fulfill that criteria as well?	24	clozapine was a very effective antipsychotic
25	A. Remember, analogy has to do with when I	25	drug, but was associated with a horrible and
	Page 159		Page 161
			iuge ivi
1	was talking about cigarette smoking. Gee, we	1	unpredictable complication called agranular
1 2	was talking about cigarette smoking. Gee, we know cigarette smoking is bad. It stands to	2	unpredictable complication called agranular cytosis.
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	Page 162		Page 164
1	looked at the evidence and did not find the	1	A. Other than other than clozapine, yes.
2	large-scale, long-term randomized human	2	It looks like the risk of weight gain and the
3	experiment that would be the absolute, positive	3	risk of diabetes and hyperglycemia is higher for
4	gold standard that would that would settle all	4	Zyprexa than some other antipsychotic agent.
5	the questions. Short of that, results are you	5	Q. And, Dr. Brancati, are you the only one
6	know, interpretations are always a little	6	who has concluded that the bulk of the scientific
7	tentative, but that's the nature of clinical	7	evidence demonstrate that Zyprexa increases the
8	research. We rarely have that kind of definitive	8	risk of hyperglycemia and diabetes?
9	evidence.	9	A. No. There are many other experts in the
10	Q. Thank you, Dr. Brancati.	10	field who share that same opinion and, in fact,
11	We've talked about some of your	11	there was a consensus conference convened by many
12	opinions. I want to make sure that we have a	12	of the leading professional societies with
13	very clear record just as what your opinions are.	13	interest in psychotic disease and in diabetes
14	So I'm going to ask you a series of questions	14	that published a Consensus Statement that
15	about your opinions.	15	expressed a very similar sentiment.
16	Do you have an opinion,	16	Q. And I'm going to pull up what's been
17	Dr. Brancati, as to whether Zyprexa use increases	17	previously marked as Plaintiff's Exhibit 2368,
18	the risk of developing type 2 diabetes compared	18	which is already introduced into evidence.
19	to people who do not use Zyprexa?	19	And is this the article that you
20	A. I do. I think Zyprexa increases the	20	were talking about, sir, or the consensus
21	risk of type 2 diabetes compared to nonusers.	21	development conference you were talking about?
22	Q. Do you have an opinion as to whether	22	A. Yes, it is.
23	Zyprexa use increases the risk of developing type	23	Q. And the am I correct that the
24	2 diabetes compared to people with severe mental	24	-
	illness who use antipsychotic drugs other than	25	of 2003?
	Page 163		Page 165
1	7		
	Zvprexa /	1	A Yes that's right
	Zyprexa? A. I do, especially in regards to certain	1 2	A. Yes, that's right.O. Okay. And the results or the report to
2	A. I do, especially in regards to certain	2	Q. Okay. And the results or the report to
2 3	A. I do, especially in regards to certain antipsychotic drugs. So in the evidence that I	2 3	Q. Okay. And the results or the report to that conference was published in this article
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	Page 166		Page 168
1	Q. And if I could direct your attention	1	mixed. They didn't want to make a call there.
2	to I believe it's the bottom of the second	2	But there were some studies that suggested that
3	page. There's a table. I believe Mr. Allen	3	those drugs might be risk factors, maybe weaker
4	showed this table, too, in his opening statement.	4	than clozapine or olanzapine, Zyprexa.
5	Could you explain for the jury what	5	And then down at the bottom,
6	it is this table shows?	6	aripiprazole and ziprasidone, two agents
7	A. Sure. This table summarizes the	7	associated with little weight gain. When they
8	deliberations of the consensus panel, which	8	looked at diabetes risk, the consensus panel
9	included experts from all those fields about	9	thought, gee, there's very little additional risk
10	about whether and which antipsychotic agents	10	of diabetes in those groups. These sorts of
11	carried the greatest metabolic risk were most	11	deliberations led the consensus panel to
12	likely to cause diabetes. Their interest in the		recommend more aggressive screening for diabetes
13	Consensus Statement was to come up with a		in users of clozapine and Zyprexa.
14	consensus on risk as a means to guide practice	14	Q. Now, this consensus panel who reached
15	as a means to guide practice.	15	those conclusions, were they experts in the field
16	They didn't urge FDA to revoke any	16	of diabetes?
17		17	
18	of the drugs from the market. Instead, they they addressed their appearent to patients and to	18	A. Yes, very much so.Q. And did this consensus conference was
19	they addressed their concerns to patients and to	19	
20	physicians to tell them to kind of give them a	20	this just an afternoon thing, or did it take place over the course of several days?
20	head's up and say, we're worried about these	20	•
22	associations. We think if you have patients on	22	A. It was several days, I believe.
	these particular drugs you should monitor more	22	Q. And did this consensus panel of experts,
23 24	frequently.		did they review the available scientific
24 25	And this was the result of their	24	literature before the conference? A. Yeah. They had there was a panel
25	deliberations. So they list clozapine on top,	25	
	Page 167		Page 169
1	olanzapine, risperidone, quetiapine,	1	that wrote the consensus and then they received
2	olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone down at the bottom.	2	that wrote the consensus and then they received presentations from other experts in the field
2 3	olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone down at the bottom. The first column is their judgment about weight	2 3	that wrote the consensus and then they received presentations from other experts in the field that attempted to synthesize all the scientific
2 3 4	olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone down at the bottom. The first column is their judgment about weight gain. Second column, risk for developing	2 3 4	that wrote the consensus and then they received presentations from other experts in the field that attempted to synthesize all the scientific literature for the purpose of the panel.
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2 3 4 5 6	olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone down at the bottom. The first column is their judgment about weight gain. Second column, risk for developing diabetes. The third column, worsening lipid profile we didn't really talk about today.	2 3 4 5 6	that wrote the consensus and then they received presentations from other experts in the field that attempted to synthesize all the scientific literature for the purpose of the panel. Q. Was Dr. David Allison one of the presenters there?
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	Page 170		Page 172
1 t	this trial?	1	Q. And is that consistent with your
2	A. I believe they are.	2	opinions?
3	Q. Were there also presentations made by	3	A. Yes.
	FDA representatives at that conference?	4	Q. I'm going to direct your attention now,
5	A. Yes.	5	sir, to the summary section of the article. And
6	Q. And were there representatives of drug	6	at the beginning of that summary, do they talk
-	companies who made presentations at that	7	about a constellation of adverse effects?
	conference?	8	A. Yes, they do.
9	A. I believe there were, yes.	9	Q. And what are the three that they
10	Q. One of which was Ms. Cavazzoni; is that	10	three adverse effects that are discussed in this
11 0	correct?	11	summary?
12	A. Yes.	12	A. They mention increased risk for obesity,
13	Q. I shouldn't misspeak. It was	13	diabetes and dyslipidemia.
14 I	Dr. Cavazzoni, correct?	14	Q. And then down at the bottom in the
15	A. (Witness nods head.)	15	summary, this panel of experts reported that,
16	THE COURT: You've got to answer	16	quote, These three adverse conditions are closely
17 d	out loud.	17	linked and their preference appears to differ
18	THE WITNESS: Yes.	18	depending on the SGA used. Clozapine and
19	Q. (BY MR. SUGGS) After hearing all of	19	olanzapine are associated with the greatest
20 t	that evidence and after reviewing all those	20	weight gain and highest occurrence of diabetes
21 p	papers and after deliberating for three days,	21	
22 t	this panel of experts essentially came up with	22	appear to have intermediate effects.
	these findings; is that correct?	23	Aripiprazole and ziprasidone are associated with
24	A. That's correct.		little or no significant weight gain or
25	Q. If I can direct your attention to some	25	diabetes or dyslipidemia, although they have not
	Page 171		Page 173
1 1	language that's in this article that talks about	1	been used as extensively as the other agents.
	the experts' review of the studies and they	2	Do you see that language, sir?
	state: Despite limitations in study design, the	3	A Yes, I do.
	data consistently show an increased risk for	4	Q Is that consistent with your opinions?
	diabetes in patients treated with clozapine or	5	A. Yes.
6 (olanzapine compared with patients not receiving	6	Q. Okay. Now, the dyslipidemia that's
	treatment with FGA's or with other SGA's.	7	referred to there, is that high cholesterol?
8	You see that language?	8	A. That's high cholesterol. In the setting
9	A. Yes.	9	of diabetes sometimes it's not so much the high
10	Q. What does FGA stand for?	10	level of the bad level, but the low level of the
11	A. First-generation antipsychotic.	11	good cholesterol, the HDL, or high density
12	Q. And SGA stands for second-generation	12	lipoprotein. So we often use that term
	antipsychotic?	13	dyslipidemia as opposed to hyperlipidemia, which
14	A. Correct.	14	means high LDL, but similar idea.
15	Q. They go on to say: The risk in patients	15	MR. SUGGS: Your Honor, may I take
	taking risperidone and quetiapine is less clear.	16	a moment and confer with my co-counsel?
	Some studies show an increased risk for diabetes,	17	THE COURT: Please.
	while others do not. The two most recently	18	MR. SUGGS: Your Honor, does the
	approved SGA's, aripiprazole and ziprasidone,	19	Court take another break?
	have relatively limited epidemiological data, but	20	THE COURT: I do take another
	available clinical trial experience with these	21	break.
	drugs has not shown an increase risk for	22	MR. SUGGS: Would it be okay if we
	diabetes.	23	took our short one now?
24	Do you see that language, sir?	24	THE COURT: I'd rather if you're
25	A. Yes.	25	close to finishing up, we finished up and then we

Page 174		Page 176
1 took our break.		I don't know what the
2 (Discussion off the record.)	2	cross-examination is going to be like, but I want
3 Q. (BY MR. SUGGS) One point Mr. Allen has	3	to be sure we have time if the jurors have any
4 suggested I go into and I agree. We talked about		questions as well with this witness. So, like I
5 the number of the cases and the case reports. I	5	said, if it's only shortly going past 1:30 so
6 believe you said that there were hundreds of 7 reports to EDA of a fightetes related events	6	that the witness can be completely done, I'd
7 reports to FDA of of diabetes-related events 9 with respect to Zupreven is that correct?		rather let him get completely done, but I'm not
8 with respect to Zyprexa; is that correct?9 A. That's correct.	8	going to go beyond five or ten minutes. If it
	9	turns out we need more time than that, we'll just
	11	end at 1:30.
11 report adverse events to FDA?12 A. In theory, they they are. Often		Mr and I can't reading my
5, 5 5	12	handwriting is it Kantra?
13 they don't. Many of them go unreported.14 O. And is it generally regarded in the	13 14	MR. KANTRA: Kantra, yes.
		MR. SUGGS: Excuse me, Your Honor.
15 field of epidemiology and in the area of16 pharmacovigilance that the number of adverse	15	I ran off with the witness' copy of his report,
	16 17	if I could just hand it to him. THE COURT: Please.
	18	MR. SUGGS: I believe Dr. Brancati
18 A. Yes, it could be only the tip of the 19 iceberg.	19	found the date of the CATIE study that you were
20 Q. I realize it's one of those things you	20	asking about.
20 Q. Treatize it's one of those times you 21 don't know what you don't know, but have there	20	THE COURT: Okay. Dr. Brancati,
22 been estimates as to what fraction or percentage	1	what's the date of the CATIE study?
23 of true adverse events ever actually get reported	23	THE WITNESS: September, '05.
24 to FDA?	24	THE COURT: Okay. Thank you.
25 A. In general, that's something I don't	25	VENIREPERSON: Your Honor, I've got
Page 175		Page 177
1 know.	1	a brief question, if I could. The study was done
1 2 0 0 kay	2	
2 Q. Okay. 3 MR SUGGS: Very good Lhave no	2	in '05, and you asked when it was published?
3 MR. SUGGS: Very good. I have no	23	in '05, and you asked when it was published? THE COURT: I asked when it was
3 MR. SUGGS: Very good. I have no 4 further questions at this time, Your Honor.	2 3 4	in '05, and you asked when it was published? THE COURT: I asked when it was published, that's correct. And my understanding
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	Page 178		Page 180
1	people with diabetes.	1	for forming your opinions, right?
2	Q. Any other benefits that might accrue?	2	A. Correct.
3	A. It's looking at a whole range of	3	Q. I take it from that that you did not
4	possible outcomes. Mortality, other forms of	4	consider or rely upon any submissions that Lilly
5	heart disease, peripheral vascular disease.	5	made to FDA in forming your opinions in this
6	Q. Okay. Have you consulted at all for	6	matter?
7	FDA?	7	A. That's right, I did not rely on those
8	A. No.	8	sources.
9	Q. You testified about a an atypical	9	Q. So I take it from that, then, that you
10	antipsychotic other than clozapine or other	10	didn't consider a submission that Lilly made in
11	than Zyprexa which is called clozapine, right?	11	July of 2000 with respect to an analysis of about
12	A. Yes.	12	
13	Q. And you mentioned that they are	13	A. That's right.
14	structurally similar, but also recognize that	14	Q. And I would assume, then, from your
15	they are different compounds, right?	15	answer that you would have not considered a
16	A. Yes.	16	submission that Lilly made in May of 2001 that
17	Q. If you were prescribed Zyprexa, you	17	included a second clinical trial analysis that
			•
18	couldn't fill it with clozapine, correct?	18	evaluated diabetes risk in patients treated with
19	A. Correct.	19	Zyprexa; is that right?
20	Q. And you mentioned that there was a fatal	20	A. That's right.
21	side effect associated with clozapine, right?	21	Q. And I would assume as well that in March
22	A. Yes.		of 2003, the Lilly submission that was made then
23	Q. And you called that agranular cytosis?	23	that evaluated diabetes-related adverse events
24	A. Yes.		after 9 million patient exposures, you wouldn't
25	Q. Can you tell the jury what that is?	25	have reviewed that as well?
	Page 179		Page 181
1	A Sure The blood is made up of many	1	
1	A. Sure. The blood is made up of many	1	A. That's correct.
2	types of cells. Red cells are the ones most	2	A. That's correct.Q. And with respect to a Lilly June, 2003
2 3	types of cells. Red cells are the ones most familiar to us, but then there are white cells,	2 3	A. That's correct.Q. And with respect to a Lilly June, 2003FDA submission regarding patients with
2 3 4	types of cells. Red cells are the ones most familiar to us, but then there are white cells, as well, the ones involved in fighting infection.	2 3 4	A. That's correct.Q. And with respect to a Lilly June, 2003FDA submission regarding patients with preexisting diabetes and whether their condition
2 3	types of cells. Red cells are the ones most familiar to us, but then there are white cells, as well, the ones involved in fighting infection. There are a variety of different flavors of the	2 3 4 5	 A. That's correct. Q. And with respect to a Lilly June, 2003 FDA submission regarding patients with preexisting diabetes and whether their condition worsened on Zyprexa, you wouldn't have reviewed
2 3 4 5 6	types of cells. Red cells are the ones most familiar to us, but then there are white cells, as well, the ones involved in fighting infection. There are a variety of different flavors of the white blood cells, and some of them are granular	2 3 4	 A. That's correct. Q. And with respect to a Lilly June, 2003 FDA submission regarding patients with preexisting diabetes and whether their condition worsened on Zyprexa, you wouldn't have reviewed that either?
2 3 4 5 6	types of cells. Red cells are the ones most familiar to us, but then there are white cells, as well, the ones involved in fighting infection. There are a variety of different flavors of the	2 3 4 5	 A. That's correct. Q. And with respect to a Lilly June, 2003 FDA submission regarding patients with preexisting diabetes and whether their condition worsened on Zyprexa, you wouldn't have reviewed that either? A. That's right.
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1 discussed it. 1 years? 2 Q. You didn't so he didn't tell you what the results of his analysis were? 3 Q. Youre aware that approximately 23 4 A. No. 3 Q. Youre aware that approximately 23 5 Q. You described diabetes as a condition which is quite prevalent in our society 7 today, right? 6 A. Mes. 5 Q. From 1980 through 2005, the number of 10 people with diabetes in this country tripled approximately? 7 6 A. Mes. 1 A. Yes. 1 1 Yes. 1 3 Q. Sound about right? From about 5 and a 14 half million to more than 16 million? 1 1 A. Yes. 1 A. Yes. 1 A. Yes. 1 A. Yes. 1 A. Yes. 1 A. Yes. 1 A. Yes. 20 Q. And sour right? 1 A. Yes. 1 A. Yes. 21 A. Roughly, yes. 2 Q. Okay. And that means that approximately 2 A. Yes. 21 Q. Mad spou methone, family history 4 Yes. 2 Q. And as you mentioned, family history 2 A. Moghly, yes. 2
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12 A. Yes. 12 Q. One of the other things that Mr. Suggs 13 Q. Sound about right? From about 5 and a 13 asked you about during the course of your 14 half million to more than 16 million? 14 testimony was risk factors for diabetes. 15 A. Yes. 15 A. Yes. 16 Q. In 2005 alone, there were about one and right? 15 A. Yes. 19 A. Yes. 16 Q. And as someone who is familiar with the 17 disabetes, you know that there are a number of different risk factors, right? 19 A. Yes. 20 Q. And general estimates for how common 21 being one of those? 20 Q. And you talked about weight gain as 21 being one of those? 22 A. Yes. 23 roughly, yes. 24 A. Yes. 24 A. Roughly, yes. 25 Q. But there are also factors, for example, 12 Page 183 Page 185 12 0. And of those, about 6 million people 1 3 Q. That would be about 1 out of every 14 Q. And as you mentioned, family history 4 people? <td< td=""></td<>
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 26 Q. And of those, 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? 4 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 astleates in a low-moving 14 tadiabetes in general is a slow-moving
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15 A. Yes, Lagree. 15 A. Correct.
16Q.And as you said, it's not always16Q.Let's talk for a minute specifically
17 accompanied by symptoms when it first presents? 17 about obesity and overweight. And as you
18A. Correct, yeah.18described it, this is probably one of the most
19Q. And that's consistent with the fact that19well-recognized risk factors for diabetes, isn't
20 there are often delays in the time that it takes 20 it?
21 from onset of diabetes to the time of actual21A.Yes.
22 diagnosis? 22 Q. And it's been known for years that
23A. That's right.23that's a risk factor for diabetes; isn't that
24 Q. And you've estimated that that's 24 right?
25 somewhere between can be between 2 and 7 25 A. Correct.

	Page 186		Page 188
1 Q. Somethi	ng you learned about as part of	1	levels within the normal range, right?
	ical school training?	2	A. Yes.
3 A. Exactly,		3	Q. Does it sound about right that a quarter
4 Q. Doctors	frequently tell patients that	4	or 25 percent of the American public has insulin
5 they need to wa	atch their weight, right?	5	resistance?
б A. Yes.		6	A. I'd say roughly, yes.
7 Q. And the	e are extensive efforts, as you	7	Q. Again, even though 25 percent of the
	ducate the public about weight	8	U.S. population has insulin resistance, 25
9 gain as well?		9	percent of the population is not diabetic, right?
10 A. Yes.		10	A. Correct.
-	ou suggested, the medical	11	Q. Again, many people who have insulin
	focused on this question		resistance don't develop diabetes?
	hin the context of atypical	13	A. Correct.
14 antipsychotics;	isn't that right?	14	Q. You also described something, I believe,
15 A. Yes.		15	as impaired fasting glucose or impaired glucose
-	Allison published that chart	16 17	tolerance. You recall that? A. Yes.
17 that you put up 18 A. Yes.	on that screen, right?	18	
	was published nine years ago	19	Q. Sometimes that's call prediabetes?A. Yes.
19 Q. And that 20 wasn't it?	t was published nine years ago,	20	Q. Another term. And the American Diabetes
20 washt h? 21 A. Yes.		21	Association recognizes that as a risk factor for
	2 out of every 3 adults in the	22	
	re either overweight or obese;	23	A. Correct.
24 isn't that right?	te entier overweight of obese,	24	Q. Represents a condition where somebody
25 A. Yes.			has blood sugar problems, but they haven't
	Dage 197		.
	Page 187		Page 189
1 O But two-		1	
_	thirds of the population in the		reached a level yet where someone has actually
2 United States is	thirds of the population in the not diabetic, right?	2	reached a level yet where someone has actually developed diabetes?
2 United States is3 A. That's co	thirds of the population in the not diabetic, right? rrect.	2 3	reached a level yet where someone has actually developed diabetes? A. Exactly.
2 United States is3 A. That's co4 Q. In fact, m	thirds of the population in the not diabetic, right? rrect. nany people who are overweight	2	reached a level yet where someone has actually developed diabetes?A. Exactly.Q. And there are about 50 million people in
2 United States is3 A. That's co4 Q. In fact, n	thirds of the population in the not diabetic, right? rrect.	2 3 4	reached a level yet where someone has actually developed diabetes?A. Exactly.Q. And there are about 50 million people in this country who have prediabetes; isn't that
 2 United States is 3 A. That's co 4 Q. In fact, n 5 or obese, as you 6 diabetes? 	thirds of the population in the not diabetic, right? rrect. hany people who are overweight said, never actually do develop	2 3 4 5	reached a level yet where someone has actually developed diabetes?A. Exactly.Q. And there are about 50 million people in this country who have prediabetes; isn't that right?
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 2 United States is 3 A. That's co 4 Q. In fact, m 5 or obese, as you 6 diabetes? 7 A. Yes. In 1 8 long-term cumu 9 calculated, it ca 10 percent. Those 11 the lifetime risk 12 for a woman 13 lifetime. For di 14 or 60 percent ov 15 Q. I underst 16 many people will 17 do develop diabila 18 A. Yes. 19 Q. You also 20 list of modifiabila 21 insulin resistance 22 A. Correct. 23 Q. And as y 24 resistance mean 	thirds of the population in the not diabetic, right? rrect. hany people who are overweight a said, never actually do develop ongitudinal studies where lative risks over a lifetime is n be as high as 50 or 60 are the figures. For example, of breast cancer is 10 percent or now 12 or 13 percent over a abetes, it can be as high as 50 ver a lifetime. and that, but there are still no are obese or overweight but never etes, right? mentioned, I believe, in the le risk factors something called ee, right?	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	 reached a level yet where someone has actually developed diabetes? A. Exactly. Q. And there are about 50 million people in this country who have prediabetes; isn't that right? A. Yes. Q. And, again, there aren't 50 million people in this country who have diabetes, right? A. Right. Q. So many of them don't ultimately go on to develop diabetes? A. Many many do ultimately over a lifespan. But, yes, when you look cross-sectionally, there's only a small fraction that actually have it, and over a period of a year or two or three it's always a small fraction. The point I was making before is that it can accumulate, so many will go on to develop diabetes, but many won't. Q. Thank you. In your work as a researcher, you've helped to design a number of

	Page 190		Page 192
1	different epidemiological studies relating to	1	backward-looking, retrospective epidemiology
2	diabetes?	2	studies are different from the randomized
3	A. Correct.	3	clinical trials?
4	Q. And if you were asked to design a study	4	A. Let me agree, but also with the
5	that was intended to look at the question of	5	footnote, because some, as I described a moment
6	whether or not an atypical antipsychotic	6	ago, some of the epidemiological studies are
7	medication or any medication for that matter was	7	prospective. For example, the cohort studies
8	leading to the development of diabetes, it would	8	identify individuals at risk for diabetes before
9	be important for you to know the extent to which	9	they have it and then look forward in the
10	risk factors were distributed among the patients	10	database. I think when you say they look
11	who were in the study, wouldn't it?	11	backwards, often even those prospective studies
12	A. Yes.	12	are done with existing databases where all the
13	Q. And that's because without that sort of	13	dust has settled, and it's a matter of the
14	information, it would be difficult to make	14	perspective taken by the investigator whether
15	reliable assessments about whether any effects	15	5
16	that might be observed were due to effects from	16	has already settled.
17	the medication or to differences among the people	17	Q. Within the context of atypical
18	who were actually being treated?	18	antipsychotics and diabetes, for example, the
19 20	A. Correct.	19	studies that you reviewed in that context were
20	Q. So if someone were designing this kind of a study that was intended to actually look at	20	all studies that were retrospective in design; isn't that right?
22	the question of whether medication causes	22	A. So the question the case reports and
23	diabetes, it would be important to do your best	23	the case series are obviously going on in
24	to make sure that the risk factors were as	24	realtime. It's individual
25	balanced as they could be among the various	25	Q. Individual patients
	Page 191		Page 193
	1030 111		
1	treatments: isn't that right?	1	
1	treatments; isn't that right?	1	A small groups. The experimental
2	A. Definitely.	2	A small groups. The experimental studies are going on in realtime as well, but the
2 3	A. Definitely.Q. But you're familiar with the fact that	2 3	A small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the
2 3 4	A. Definitely.Q. But you're familiar with the fact that within the databases that are used in the context	2 3 4	A small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the cross-sectional studies, yes, were generally done
2 3	A. Definitely.Q. But you're familiar with the fact that within the databases that are used in the context of these epidemiology studies that we've often	2 3	A small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the cross-sectional studies, yes, were generally done with existing databases where the dust had
2 3 4 5	A. Definitely.Q. But you're familiar with the fact that within the databases that are used in the context of these epidemiology studies that we've often talked about, that many of the risk factors we've	2 3 4 5	A small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the cross-sectional studies, yes, were generally done with existing databases where the dust had settled and it was a matter of the epidemiologist
2 3 4 5	 A. Definitely. Q. But you're familiar with the fact that within the databases that are used in the context of these epidemiology studies that we've often talked about, that many of the risk factors we've described, whether they be family history or 	2 3 4 5	A small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the cross-sectional studies, yes, were generally done with existing databases where the dust had settled and it was a matter of the epidemiologist looking for patterns in the existing data.
2 3 4 5 6 7	 A. Definitely. Q. But you're familiar with the fact that within the databases that are used in the context of these epidemiology studies that we've often talked about, that many of the risk factors we've described, whether they be family history or physical inactivity or any number of other 	2 3 4 5 6 7	A small groups. The experimental studies are going on in realtime as well, but the cohort studies and the case-control studies, the cross-sectional studies, yes, were generally done with existing databases where the dust had settled and it was a matter of the epidemiologist
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	Page 194		Page 196
1	article that agrees with that proposition; isn't	1	could Mike, if you could pull out the if
2	that right?	2	sustained language.
3	A. You're referring to the article with	3	See the sentence at the end there?
4	the article from the precursor study?	4	A. Yes.
5	Q. This would be your actually, why	5	Q. So when I asked you the question of
6	don't we go ahead and just pull that up and make	6	whether or not you had actually published on this
7	it easier to talk about it. If we could pull up	7	issue and written in accordance with the
8	No. 156.	8	conventional medical wisdom, the answer is that
9	A. Sure. Yes.	9	in fact you have published on precisely that
10	Q. And if we can go to the last sentence of	10	point?
11	the first full paragraph on the I believe it's	11	A. Yes.
12	the next-to-last page of the document.	12	Q. Okay. Now, nearly all of the published
13	THE COURT: For what it's worth,	13	articles relating to weight gain and risk of
14	and I don't know if it's worth very much, my	14	diabetes are that you relied upon in forming
15	screen isn't coming up.	15	your opinions are articles that come from
16	MR. KANTRA: Sorry?	16	long-term studies, right?
17	THE COURT: I said, for what it's	17	A. Correct.
18	worth, my screen with the articles is not coming	18	Q. These are articles that or studies
19 20	up.	19	that look at patients who may be treated for 5,
20	MR. KANTRA: Oh, is that right?	20 21	10, 15, sometimes even 20 years? A. Yes.
22	I'm happy to provide a copy. THE COURT: Never mind.	22	Q. And these are studies in these
23	Q. (BY MR. KANTRA) Sir, do you want a copy	23	studies that you've relied upon are studies in
24	of the article, or are you fine looking at the	24	people who have gained weight for any reason,
25	monitor as well?		right?
	Page 195		Page 197
			Faye 12/
1		1	
1	A. No, I'm good.	1	A. Yes.
2	A. No, I'm good.Q. If you look at the article, this is an	2	A. Yes.Q. They're not limited to patients who are
2 3	A. No, I'm good.Q. If you look at the article, this is an article which is entitled Body Weight Patterns		A. Yes.Q. They're not limited to patients who are being treated with atypical antipsychotics?
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Page 19	Page 200
1 know, 45 or 50, and look at weight gains over	1 Q. Where the risk factors are listed?
2 that period. Because, historically, it took that	2 A. Yes.
3 much time to put on weight. And so we know a lo	3 Q. For diabetes?
4 more about sustained sustained weight gain.	4 A. Yes.
5 Part of the rationale of the paper	5 Q. And you're familiar with those screening
6 that that we published from the Johns Hopkins	6 guidelines as they currently exist?
7 precursor study is that conventional wisdom was	7 A. I haven't reviewed them specifically to
8 that it was really 10 or 15 years worth of weight	8 prepare for today, but, yes, generally.
9 gain or 20 that made a difference. We had 30 or	9 Q. Generally you're familiar with it. And
10 40 years of followup, so we were stretching the	10 Zyprexa and atypical antipsychotics have never
11 importance of weight on the long end. But you're	11 appeared on that list of risk factors in the
12 right, you're asking about stretching it on the	12 screening guidelines; isn't that right?
13 short end. You know, we know less.	13 A. Correct.
14 Q. And my point is: You've not done	14 Q. Are you familiar with what a Consensus
15 research that's looked at that narrow time frame	15 Statement reflects? Generally, what it's
16 of weight gain within a small number of months	16 intended to do? 17 A. Yes.
 17 A No. 18 Q and whether it leads to the 	17 A. Yes.18 Q. And you're familiar with the fact that a
19 development of diabetes, right?	19 Consensus Statement does not represent the
20 A. No, I've done the inverse of that which	20 official position of the American Diabetes
21 is	21 Association?
22 Q. I'm not asking about that, the weight	22 A. That's correct.
23 loss. I'm asking specifically about the weight	23 MR. KANTRA: Go ahead and pull up
24 gain piece. You've not done that work?	24 2000 Yale, 2001. And if we could go I
25 A. No.	25 think it's the fourth page of that document.
Page 19	Page 201
iuge iv	Page 201
1 Q. Let me ask you, specifically, about the	1 Q. (BY MR. KANTRA) While we're getting
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	Page 202		Page 204
1	A. Yes.	1	Q. And among other things, what I
2	Q. And in the course of this letter, one of	2	understand is that you teach students who are
3	the things that they did was to address the issue	3	learning about epidemiology?
4	that had been raised by the Consensus Statement	4	A. Yes.
5	of the relationship whether there was a	5	Q. And one of the things that you do is you
6	relationship between the weight gain that occurs	6	help to educate them about this how we look at
7		7	-
	while being treated with an atypical	8	evidence around the issue of causation, right? A. Yes.
8	antipsychotic and the ultimate development of		
9	diabetes, right?	-	Q. And in helping to teach them about this
10	A. Yes.	10	evidence relating to causation, you help teach
11	Q. Okay.	11	5
12	MR. KANTRA: Can you pull up that		was up on the screen earlier, don't you?
13	one paragraph on the bottom left? And if you can	13	A. Yes.
14	go, Mike, to the sentence that begins with	14	Q. And that hierarchy of evidence would run
15	"although." And that sentence and the sentence		from the case reports that you talked about
16	that follows that.	16	initially, up through these observational
17	Q. (BY MR. KANTRA) So I want to just I	17	epidemiological studies, to clinical trials or
18	want to just take a look at this sentence, and in	18	experimental trials at the top?
19	particular what it says here is that, Although	19	A. Yes.
20	weight gain may be a factor in explaining the	20	Q. Okay. And you had mentioned a couple of
21	increased diabetes risk for SGA's, DNDP which	21	times that sometimes work is done with animals to
22	is that's the part of the FDA that we were	22	evaluate safety-related issues, right?
23	just talking about, right?	23	A. Correct.
24	A. Yes.	24	Q. And those types of studies are helpful
25	Q is not aware of evidence proving that	25	for identifying ideas for future studies in
			· ·
	Page 203		Page 205
1	the treatment emergent diabetes risk for these	1	humans, right?
1 2		1 2	
	the treatment emergent diabetes risk for these		humans, right?
2	the treatment emergent diabetes risk for these drugs is wholly or in part due to	2	humans, right? A. They could be done for a variety of
2 3	the treatment emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. And it goes on	2 3	humans, right?A. They could be done for a variety of purposes, but that would be one of them.
2 3 4	the treatment emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. And it goes on to say that although weight gain is widely	2 3 4	humans, right?A. They could be done for a variety of purposes, but that would be one of them.Q. Among other reasons?
2 3 4 5 6	the treatment emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. And it goes on to say that although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial and	2 3 4 5	humans, right?A. They could be done for a variety of purposes, but that would be one of them.Q. Among other reasons?A. Yes.Q. And they provide us with ideas,
2 3 4 5 6	the treatment emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. And it goes on to say that although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial and that's another way of saying the experimental	2 3 4 5 6 7	 humans, right? A. They could be done for a variety of purposes, but that would be one of them. Q. Among other reasons? A. Yes. Q. And they provide us with ideas, hypotheses, but they need to be confirmed in
2 3 4 5 6 7 8	the treatment emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. And it goes on to say that although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial and	2 3 4 5 6 7	 humans, right? A. They could be done for a variety of purposes, but that would be one of them. Q. Among other reasons? A. Yes. Q. And they provide us with ideas, hypotheses, but they need to be confirmed in humans, ultimately, don't they?
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	Page 206		Page 208
1	A. Correct.	1	who develops diabetes and then is taken off drug
2	Q. Okay. With respect to these kinds of	2	with improvement after that point, there is what
3	studies, what we don't have in contrast to the	3	is known as a spontaneous remission sometimes,
4	experimental studies or the clinical trials that	4	right?
5	you've talked about, is what's called a control	5	A. Rare.
6	group, right?	6	Q. But it happens?
7	A. That's right.	7	A. Yes, I I've not seen it in my
8	Q. And so what we don't know with respect	8	practice, but it could happen.
9	to either the dechallenge cases or the	9	Q. But you're aware of it?
10	rechallenge cases, for that matter, is how many	10	A. Yes.
11	patients were taken off drug having developed it	11	Q. It's been reported in the literature?
12	without an improvement, right?	12	A. Yes.
13	A. Yes.	13	Q. And you would agree with me that these
14	Q. Similarly, what we don't know is how	14	individual case reports that we've been talking
15	many patients were put back on drug, but then	15	about are different in kind from the clinical
16	didn't redevelop the event?		trials that you've described in this in this
17	A. Right.	17	hierarchy of evidence, right?
18	Q. That's just information that we don't	18	A. Yes.
19	have the benefit of?	19	Q. And they would be very different in
20	A. That's right.	20	terms of the quality of the evidence from studies
21	Q. And one of the reasons why it's helpful	21	that are designed specifically to look at the
22 23	to have information like what I've just	22	question of whether there is a mechanism by which
23 24	described, information about numbers of patients who didn't develop a particular adverse event	24	a drug can result in causing diabetes? A. Yes.
25	after dechallenge or rechallenge, is that it	25	Q. If we look back at the case reports that
		23	
	Page 20/		Page 209
1	Page 207	1	Page 209
1	helps us to identify a rate at which something is	1	have been published, what I recall from your
2	helps us to identify a rate at which something is occurring, right?	1 2 3	have been published, what I recall from your testimony is that you said that the first case
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 9 20 21 22 23	 helps us to identify a rate at which something is occurring, right? A. Correct. Q. And in identifying what that rate is, it helps us understand whether we're seeing something that is in excess of what we would expect to see or consistent with what we would expect to see? A. That's right. Q. With dechallenge and rechallenge cases, we don't always know, many times we don't know, whether, in fact, there have been changes in a patient's lifestyle or medications or medical history that may affect the outcome of it? A. Could be, yes. Q. Put differently, perhaps, the reports that that are published in the literature or submitted to FDA depend, in part, on the quality and the knowledge and experience of the physician who's actually making the report? A. Yes. Q. And how familiar they are with the relevant issues? 	4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	 have been published, what I recall from your testimony is that you said that the first case reports relating to Zyprexa and cases of diabetes were approximately 10 years ago, right? A. Yes. Q. You said mid-'90s, I believe? A. Yes. Q. And I believe what you told us was that case reports provide a basis, again, for generating ideas, raising awareness of physicians, alerting them to potential issues that they might need to pay attention to? A. Yes, in general. Occasionally they're so persuasive that they constitute evidence in themselves, for example, a very unusual type of complication that would otherwise rarely or never occur. With diabetes, as you pointed out, it's common enough in everyday practice that it's hard to tell for certain from case reports alone. Q. You would agree with me that between 1998 when the first case report for Zyprexa was published, and the spring of 2002, the evidence that was available with respect to the issue of
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 9 20 21 22	 helps us to identify a rate at which something is occurring, right? A. Correct. Q. And in identifying what that rate is, it helps us understand whether we're seeing something that is in excess of what we would expect to see or consistent with what we would expect to see? A. That's right. Q. With dechallenge and rechallenge cases, we don't always know, many times we don't know, whether, in fact, there have been changes in a patient's lifestyle or medications or medical history that may affect the outcome of it? A. Could be, yes. Q. Put differently, perhaps, the reports that that are published in the literature or submitted to FDA depend, in part, on the quality and the knowledge and experience of the physician who's actually making the report? A. Yes. Q. And how familiar they are with the 	4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	 have been published, what I recall from your testimony is that you said that the first case reports relating to Zyprexa and cases of diabetes were approximately 10 years ago, right? A. Yes. Q. You said mid-'90s, I believe? A. Yes. Q. And I believe what you told us was that case reports provide a basis, again, for generating ideas, raising awareness of physicians, alerting them to potential issues that they might need to pay attention to? A. Yes, in general. Occasionally they're so persuasive that they constitute evidence in themselves, for example, a very unusual type of complication that would otherwise rarely or never occur. With diabetes, as you pointed out, it's common enough in everyday practice that it's hard to tell for certain from case reports alone. Q. You would agree with me that between 1998 when the first case report for Zyprexa was published, and the spring of 2002, the evidence

	Dama 210		Dorro 010
-	Page 210		Page 212
1	MR. SUGGS: Object, Your Honor.	1	2002 was sufficient to support the conclusion
2	THE COURT: What's the basis for		that Zyprexa causes diabetes, right?
3	the objection?	3	A. Right, the published literature which is
4	MR. SUGGS: Objection to the form.	4	what I review, yeah.
5	He's talking about evidence. What evidence? The	5	Q. Published literature, exactly.
6	publicly-available evidence or including what	6	Let's talk for a minute about
7	Lilly knew?	7	epidemiology studies as you've defined them. The
8	THE COURT: You're referring to the	8	limitations of these kinds of studies, most
9	case studies that	9	precisely or perhaps most importantly relate to
10	MR. KANTRA: I said the published	10	the issue of randomization, right?
11	literature. I believe I said that.	11	A. I'm sorry? Could you restate that?
12	THE COURT: I'll overrule the	12	Q. Let me phrase it again.
13	question. Do you understand the question?	13	As you think about the difference
14	THE WITNESS: Yes, I do.	14	between what you call these experimental studies
15	A. You know, I think we had some of this	15	or clinical trials
16	discussion during the deposition. I didn't	16	A. Yes.
17	structure the report in terms of time sequence,	17	Q and these database studies or these
18	so I took all the data up through the end of 2006	18	case-control cohort studies?
19	and made judgments in totality. I do recall	19	A. Observational epidemiological study.
20	offhand that by 2002 there was a one paper	20	Q. Observational epidemiological studies.
21	that compiled several hundred case reports that I		If we're thinking about the contrast between
22	referenced a few minutes ago verbally with the	22	those two things, one of the most important
23	challenge and the dechallenge and the	23	distinctions is the fact that the experimental
24	rechallenge, but I can't	24	studies or the clinical trials have the benefit
25	Q. (BY MR. KANTRA) Just to be clear, just	25	of randomization, whereas the observational
	Page 211		Page 213
1	so you understand what I'm asking	1	epidemiological studies do not, right?
2	MR. SUGGS: Your Honor, can we have	2	A. Exactly.
3	the witness be allowed to finish his answer?	3	Q. Okay. And randomization refers to the
4	THE COURT: I don't think were	4	random assignment of patients to different
5	you finished or	5	treatment groups, right?
6	THE WITNESS: Yeah.	6	A. That's correct.
7	THE COURT: Okay. Go ahead.	7	Q. And I think you described it as patients
8	Q. (BY MR. KANTRA) The article or the	8	are assigned, essentially, on the flip of a coin,
9	analysis that you've referenced in regards to	9	right?
10	those those various case reports, separate and	10	A. That's right.
11	apart from an analysis of case reports, if we're	11	Q. And the benefit of doing it that way, as
12	talking about cross-sectional studies, cohort	12	we talked about earlier, is the fact that you
13	studies, those sorts of things within the	13	want to make sure that as much as possible people
14	epidemiological sphere, you're not aware of any	14	are similarly situated in the two treatment
15	epidemiology studies relating to Zyprexa and	15	groups so that you can assess whether or not an
16	diabetes that were published before the spring of	16	effect is the result of a medication or something
17	2002; isn't that right?	17	else?
18	A. That sounds right. No, the vast	18	A. That's right.
19	majority were after that time. I can't recall	19	Q. And without randomization, then,
20	offhand whether there were any before that time.	20	scientists who are studying the risk of whether
21	Q. Sitting here today, you don't you	21	diabetes occurs in patients on certain
22	don't remember any?	22	medications at higher rates can't be sure of
23	A. No.	23	whether they the patients were comparable with
25	Ω And you've not offered any sort of		respect to their baseline risk factors for

Q. And you've not offered any sort ofopinion that the literature as it existed as of

respect to their baseline risk factors fordiabetes?

	Page 214		Page 216
1	A. That's right.	1	isn't that right?
2	Q. Put differently, scientists can't be	2	A. That's right.
3	sure that they're dealing with a level playing	3	Q. One way to evaluate whether or not
4	field?	4	diabetes has occurred is to look at various
5	A. That's correct.	5	thresholds or cutoff points, right?
6	Q. Okay. And among other things, the	6	A. Cutoff points of glucose you mean?
7	absence of randomization in observational	7	Q. Right. Exactly.
8	epidemiological studies is one of the reasons why	8	A. Yes.
9	an assessment of causation requires a look across	9	Q. So, for example, when you spoke earlier
10	all of the data, including the experimental	10	about the way in which diabetes is diagnosed, one
11	studies, right?	11	of the things you said is that if it's a random
12	A. Yes.	12	blood sugar level above 200 with symptoms, that
13	Q. You wouldn't want to limit yourself to		would support a diagnosis of diabetes?
14	just one bucket of evidence, right?	14	A. That's right.
15	A. That's right, although, as I pointed out	15	Q. Similarly, if you have a fasting blood
16	with the smoking example, sometimes experimental	16	glucose level that is 126 or higher, that would
17	data in humans is hard to come by. Sometimes we	17	be another basis for making a diagnosis of
18	do put all our eggs in the observational basket.	18	diabetes?
19	But, in general, yes, when we can, we like to	19	A. That's right.
20	have experimental evidence as well.	20	Q. When I say thresholds, I'm referring to
21	Q. And here, certainly you didn't limit	21	those kinds of cut points and, similarly, one
22	your review of the evidence just to the	22	could also look at prediabetes as a category of
23	epidemiological studies, right?	23	cases, right?
24	A. Right.	24	A. Yes.
25	Q. You looked beyond that to the	25	Q. So there we'd be interested in
	.		
	Page 215		Page 217
1	experimental studies as well?	1	identifying patients, for example, if they were
1 2	experimental studies as well? A. Yes.	1 2	identifying patients, for example, if they were fasting, had values between 100 and 125, right?
	•	1 2 3	
2	A. Yes.	2	fasting, had values between 100 and 125, right?
2 3	Â. Yes.Q. In the context of these observational	2 3	fasting, had values between 100 and 125, right? A. Yes.
2 3 4	 A. Yes. Q. In the context of these observational epidemiological studies, one of the things that researchers try and do from time to time, or many 	2 3 4	fasting, had values between 100 and 125, right?A. Yes.Q. And so if we're interested in seeing
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2 3 4 5 6	 A. Yes. Q. In the context of these observational epidemiological studies, one of the things that researchers try and do from time to time, or many times try and do, is to go back and try and balance the groups after the fact, right? Adjust 	2 3 4 5 6	fasting, had values between 100 and 125, right?A. Yes.Q. And so if we're interested in seeing outcomes, whether it's people with prediabetes or
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	 A. Yes. Q. In the context of these observational epidemiological studies, one of the things that researchers try and do from time to time, or many times try and do, is to go back and try and balance the groups after the fact, right? Adjust for various ways in which the groups might be imbalanced? A. Yes. Q. But in terms of being able to adjust for differences in risk factors that might exist between the two groups, this may be evident, but you can only do that if you have the information about the risk factors? A. That's right. Q. Your results are only as good as the database with which you're working? A. Correct. 	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	 fasting, had values between 100 and 125, right? A. Yes. Q. And so if we're interested in seeing outcomes, whether it's people with prediabetes or diabetes, one way to evaluate that is to look at these categorical cut points, these significant clinical thresholds? A. Yes. Q. Okay. Another way that scientists can go about evaluating whether or not somebody in a particular analysis might have diabetes is to look at the question of whether they're actually being treated with medication for diabetes? A. That's correct. Q. So, for example, if someone is being treated with insulin, that might be something that would be of interest? A. Yes.
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	Page 218		Page 220
1	Q. That would be another way, an acceptable	1	regard, the human experiments, the trials are at
2	way, a recognized way of looking at whether or	2	the top of the pyramid.
3	not someone had diabetes?	3	The trouble is, and I think we see
4	A. Yes.	4	it in the CATIE study, is that trials are hard to
5	Q. And then there's also what is sometimes	5	mount in large numbers for long periods of time.
6	referred to as a continuous analysis?	6	So frequently evidence we have from experiments
7	A. Yes.	7	or trials is limited in time. Might be only
8	Q. That would be equivalent to what is	8	weeks or months. When you go into a study with a
9	called sometimes an average change analysis,	9	time frame of only weeks or months, it may not be
10	right?	10	reasonable to pin your hypothesis on the
11	A. Uh-huh, yes.	11	development of a condition like diabetes or heart
12	Q. Meaning that put differently, the	12	disease. In those settings, even though we look
13	question is, on average, how how much do	13	at all three end-points for information, my sense
14	patients' blood sugar levels go up while they're	14	going into the study, just reading about the
15	on a particular medication?	15	design before reading about the results, was that
16	A. That's right.	16	the most precise continuous measures would be the
17	Q. And that was one of the things that you	17	most informative.
18	talked about with respect to the CATIE study,	18	Q. And that's actually an interesting
19	right?	19	point, because there are studies, and I believe
20	A. Yes.	20	you mentioned this as well during your direct
21	Q. One of the things you noted in there was	21	testimony, that if we look at continuous measures
22	that there were increases in blood glucose	22 23	or these average change measures, you're aware
23 24	levels? A Yes.	23 24	that within the context of clinical trials that
24 25		24	compare Zyprexa with other atypical antipsychotics, there are studies that compare,
25		25	
	Page 219		Page 221
1	A1C's a little bit?	-	for example, Zyprexa with Geodon in a direct sort
2	A. Yes.	2	of head-to-head comparison.
3	Q. And you recalled that in that study as	3	Are you familiar with those studies?
4 5	well they also looked at whether or not there were significant differences in patients who were	4	sinces/
	were significant differences in Datients who were	5	
	•	5	A. Yes.
6	treated with new antidiabetic medications?	5 6 7	A. Yes.Q. And you're familiar with the fact that
6 7	treated with new antidiabetic medications? A. Yes.	6 7	A. Yes.Q. And you're familiar with the fact that there are studies out there that made that direct
6 7 8	treated with new antidiabetic medications?A. Yes.Q. And by that measurement they didn't	6 7 8	A. Yes.Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did
6 7 8 9	treated with new antidiabetic medications?A. Yes.Q. And by that measurement they didn't actually find a significance difference among the	6 7 8 9	 A. Yes. Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in
6 7 8 9 10	treated with new antidiabetic medications?A. Yes.Q. And by that measurement they didn't actually find a significance difference among the treatment groups?	6 7 8 9 10	 A. Yes. Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in these average glucose levels?
6 7 8 9 10 11	treated with new antidiabetic medications?A. Yes.Q. And by that measurement they didn't actually find a significance difference among the treatment groups?A. I think that's right, yes.	6 7 8 9 10 11	 A. Yes. Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in these average glucose levels? A. Especially in some of the shorter-term
6 7 8 9 10 11 12	 treated with new antidiabetic medications? A. Yes. Q. And by that measurement they didn't actually find a significance difference among the treatment groups? A. I think that's right, yes. Q. And all of these three measurements, 	6 7 9 10 11 12	 A. Yes. Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in these average glucose levels? A. Especially in some of the shorter-term studies, but, yes.
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6 7 8 9 10 11 12	 treated with new antidiabetic medications? A. Yes. Q. And by that measurement they didn't actually find a significance difference among the treatment groups? A. I think that's right, yes. Q. And all of these three measurements, whether we talk about these clinical thresholds, this categorical analysis they're sometimes 	6 7 9 10 11 12 13	 A. Yes. Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in these average glucose levels? A. Especially in some of the shorter-term studies, but, yes.
6 7 8 9 10 11 12 13 14	 treated with new antidiabetic medications? A. Yes. Q. And by that measurement they didn't actually find a significance difference among the treatment groups? A. I think that's right, yes. Q. And all of these three measurements, whether we talk about these clinical thresholds, 	6 7 8 9 10 11 12 13 14	 A. Yes. Q. And you're familiar with the fact that there are studies out there that made that direct comparison between those two medications and did not find statistically significant differences in these average glucose levels? A. Especially in some of the shorter-term studies, but, yes. Q. And, indeed, in studies that went up to six months?
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	Page 222		Page 224
1	significantly different between the two groups,	1	talked about earlier?
2	again, over studies that go out to a period of	2	A. Yes.
3	six months?	3	Q. And that's sometimes referred to as a
4	A. That's correct, and one of the problems	4	euglycemic clamp study, isn't it?
5	with some of those studies that I mentioned	5	A. Yes.
		6	
6	before is that to the extent that they use		Q. What's done in those kinds of studies is
7	nonfasting glucose, that they mix fasting and	7	to ask the question of whether, again, in an
8	nonfasting, it does introduce some noise in those	8	experimental kind of setting there was an effect
9	studies. That's part of the reason I spent some	9	of the drug such that people's insulin resistance
10	time talking about the hemoglobin A1C, because I	10	actually got worse as a result of taking the
11	was impressed that that was an end-point that		drug?
12	would be more stable and more impervious to the	12	A. Yes.
13	noise introduced by getting blood sugar	13	Q. And you're familiar with the fact that
14	measurements different times of the day.	14	there were two clinical trials that Lilly
15	Q. Understood, but if we're working with	15	conducted that looked at those issues?
16	the data that we have	16	A. Yes.
17	A. Yes.	17	Q. And those studies would fall into the
18	$Q_{$	18	bucket of evidence that you described as being
19	head-to-head studies when we looked at the	19	experimental, right?
20	measurements of glucose disregulation that	20	A. Yes.
21	existed, they didn't find differences there?	21	Q. And the results of those studies, each
22	A. In some studies, yes, that's right.	22	of them, found that there was no evidence of a
23		23	
			1 ,
24	you evaluated a couple of studies that are known	24	right, or increasing insulin resistance?
25	as clamp studies, didn't you?	25	A. I think that's right, and my
	Page 223		Page 225
1		1	
1	A. Yes.	1	recollection was both of those clamp studies,
2	A. Yes.Q. And a clamp study is a study which is,	2	recollection was both of those clamp studies, which were well done, were both short-term, I
2 3	A. Yes.Q. And a clamp study is a study which is, as we talked at the beginning, there are things	2 3	recollection was both of those clamp studies, which were well done, were both short-term, I think, with two or three weeks or so, if I
2 3 4	A. Yes.Q. And a clamp study is a study which is, as we talked at the beginning, there are things that are called mechanistic studies, right?	2 3 4	recollection was both of those clamp studies, which were well done, were both short-term, I think, with two or three weeks or so, if I recall properly.
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2 3 4 5 6	 A. Yes. Q. And a clamp study is a study which is, as we talked at the beginning, there are things that are called mechanistic studies, right? A. Yes. Q. And those are studies that are done to 	2 3 4 5 6	recollection was both of those clamp studies, which were well done, were both short-term, I think, with two or three weeks or so, if I recall properly.Q. Done done on an acute basis, right?A. Done on an acute basis. So, I thought
2 3 4 5 6 7	 A. Yes. Q. And a clamp study is a study which is, as we talked at the beginning, there are things that are called mechanistic studies, right? A. Yes. Q. And those are studies that are done to help evaluate whether there is an explanation by 	2 3 4 5	recollection was both of those clamp studies, which were well done, were both short-term, I think, with two or three weeks or so, if I recall properly.Q. Done done on an acute basis, right?A. Done on an acute basis. So, I thought those were smart studies to do. Those studies
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	Page 226		Page 228
1	the clinical trials and look at the issue of	1	have a few questions.
2	whether or not there is there are	2	REDIRECT EXAMINATION
3	statistically significant differences in looking	3	Q. (BY MR. SUGGS) First of all, that issue
4	at diabetes as an outcome, the event of diabetes,	4	with respect to the clamp studies that were done?
5	you do not see significant differences there, do	5	A. Yes.
6	you?	6	Q. What was the purpose of those studies in
7	A. You wouldn't expect it given the	7	terms of their design? What were they looking
8	duration and the size and you don't see it.	8	at?
9	Q. And you don't see it.	9	A. My impression is they were really
10	MR. KANTRA: Can I have just one	10	looking at the the question of whether there's
11	second, Your Honor, to consult?	11	a direct and immediate ill effect of Zyprexa on
12	THE COURT: Sure.		the pancreas and its ability to secrete insulin
13	(Discussion off the record.)		or on the insulin-sensitive tissues. And to the
14	MR. KANTRA: Dr. Brancati, thank		extent that they're negative, they suggest that
15	you for your time.		there is no direct effect. Than's why I said a
16	THE COURT: Mr. Suggs.	16	moment ago, it made me think more of longer-term
17	MR. SUGGS: Your Honor, may I	17	
18	approach the bench?	18	sophisticated clamp study, it's limited by the
19	THE COURT: Sure.	19	people who are in it and by the duration of the
20	MR. SUGGS: I think that they	20	
21	opened up the door with respect to the 2007 label	21	So if the effects of Zyprexa take
22	change. They talked about the letter from the		longer than a few weeks to develop, even the
23	FDA after the 2003 Consensus Statement saying	23	•
24			investigators won't detect that. But it does
25	MR. KANTRA: That was 2004. I'm		rule out an acute toxic effect, which was one of
25	Page 227	25	Page 229
1		-	
1	sorry.		the possibilities and those well-done studies
2	MR. SUGGS: saying that they		rule that out.
3	disagreed with the consensus. It was 2004; the	3	Q. And do those studies rule out the effect
3 4	disagreed with the consensus. It was 2004; the publication was 2004. Their letter was some	3 4	Q. And do those studies rule out the effect of Zyprexa by indirect means by affecting weight
3 4 5	disagreed with the consensus. It was 2004; the publication was 2004. Their letter was some months after the publication of the study. They	3 4 5	Q. And do those studies rule out the effect of Zyprexa by indirect means by affecting weight over the long term?
3 4 5	disagreed with the consensus. It was 2004; the publication was 2004. Their letter was some months after the publication of the study. They said they disagreed with the Consensus Statement.	3 4 5	Q. And do those studies rule out the effect of Zyprexa by indirect means by affecting weight over the long term?A. No, and that's why I said that looking
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1	MR. SUGGS: Thank you.	1	I've already ruled on this, Mr. Allen.
2	THE COURT: Anything further, Mr.	2	MR. ALLEN: This is what they're
3	Kantra?	3	doing is creating they say, we gave it to FDA,
4	MR. KANTRA: No re-cross, Your	4	we gave it but they didn't give everything to
5	Honor.	5	the FDA.
6	THE COURT: Do any of the members	6	THE COURT: I'm not going to give
7	of the jury have any questions? If you do, what	7	that question because I think it's outside the
8	I'd like you to do is what I instructed you	8	scope of his testimony about the validity of
9	previously, is write your question down on a	9	I don't have any problem with that
10	piece of paper and hand them up to Mr. Borneman.	10	one either.
11	I just want to make clear by asking that	11	MR. ALLEN: That's fine.
12	question, don't feel you have to give me	12	MR. KANTRA: Fine. They need to be
13	questions. It's totally up to you.	13	educated on that.
14	Ms. Wallace, do you have any	14	THE COURT: I'll ask him the
15	coming?	15	questions, then, and if we need to have follow-up
16	VENIREPERSON: I have one. I just	16	we will.
17	have to look for my	17	Three of the four questions that
18	THE COURT: Who is this one from,	18	I've received, I'm going to ask one of them. It
19	Mark?	19	will certainly be appropriate later on in the
20	THE CLERK: I think it was from	20	trial, but not from this witness.
21	Ms. Mitchell, but I'm not positive that's	21	Doctor, can you provide the name
22	right, it was from Ms. Shepherd, 12.	22	for I'm going to have trouble aripiprazole
23	THE COURT: Would counsel approach,	23	and ziprasidone such as olanzapine and Zyprexa?
24	please?	24	In other words, what's the trade name of those
25	Do you have any comments with that	25	other two generic names, if you know?
	Page 231		Page 233
1	one? Any objections to that?	1	THE WITNESS: You know, I'm trained
2	MR. KANTRA: Yeah, that's a fair	2	at Hopkins, we use the generic names all the
3	question.	3	time. It's a matter of discipline, so that it
4	THE COURT: I don't think I have	4	diminishes our exposure to the brand names which
5	problems with that one. I don't know whether he	5	are advertised. So I would need to refer to be
6	can answer it, but	6	sure.
7	MR. ALLEN: I don't know he can	7	THE COURT: Okay. Let me ask
8	ask the question	8	counsel: Would there be any problem if maybe
9	THE COURT: I'll ask him if he	9	tomorrow you give a stipulation to the jury as to
10	knows, okay?	10	what the trade names of these other
11	MR. SUGGS: I'll ask him.	11	MR. ALLEN: I can do it right now.
12	THE COURT: I've got some concerns	12	THE COURT: Well, I want to make
13	that it's appropriate for him to answer the	13	sure that Lilly agrees with what you're going to
14	question.	14	say, Mr. Allen, and stuff. So give it to me in
15	MR. ALLEN: No.	15	the form of a stipulation, and I'll read it to
16	MR. FIBICH: They don't want that	16	the jury tomorrow so that everybody knows what
17 10	asked because they got him they tried to get	17	everybody agrees on.
18 19	him to say, you know, you didn't look at our	18	This is if you know this: What
	submission, you didn't look at our submission.	19	is known about why mentally ill individuals have
20 21	Your Honor, here's the fact. In January of 2007,	20 21	a greater propensity to weight gain as opposed to
21 22	when they got the the FDA got the information, they made them change the warning. Their	21	the general population? THE WITNESS: That's a good
23	submission was fraudulent.	23	question. I'll interpret it as apart from the
24	THE COURT: And, again, you can ask	24	use of antipsychotic medicines.
25	that question from other people, but that's 2007.	25	THE COURT: That's I would like
		-	

	Page 234		Page 236
1	you to interpret it that way.	1	(Jury out.)
2	THE WITNESS: Yeah. It could be	2	THE COURT: Please be seated again.
3	that they're exercising less or they're in	3	We're outside the presence of the jury. Anything
4	environments where there's nothing else to do but	4	we need to immediately take up before we leave
5	eat more. They're confined. That's one of the	5	for the day?
6	thoughts, in fact, one of the hunches we're	6	MR. ALLEN: Aripiprazole is Abilify
7	playing in a study at Hopkins aimed at improving	7	and ziprasidone is Geodon.
8	diet and physical activity in group homes where	8	THE COURT: Again, give me
9	many individuals with severe mental illness spend	9	something to read in the morning and I'll read it
10	their daytimes.	10	to the jury. If you'll give me a pronunciation
11	THE COURT: And then the last	11	guide, it might be helpful as well. I just want
12	question I'm going to ask you from the jurors is:	12	to make Mr. Allen, keeping you from giving
13	Did Lilly study I think that means the two	13	what you just said, I wasn't in any ways casting
14	clamp studies address weight gain and its	14	aspersions or doubting your veracity. I just
15	long-term effects?	15	feel I had to give Lilly a chance to agree with
16	THE WITNESS: Well, no. The clamp	16	you.
17	studies were designed to be short-term studies of	17	MR. ALLEN: I can't believe it
18	the immediate physiologic effects of the drug, so	18	takes them 24 hours to agree with something like
19	there was really no way it could study long-term	19	that.
20	weight gain. The I presented the best data	20	THE COURT: I suspect it won't.
21	that I saw on weight gain, which was from that	21	And, again, if you all as I take it, there's
22	meta analysis. That was a ten-week only a	22	nothing critical I have to rule on with
23	ten-week interval, though.	23	deposition testimony or things tomorrow. So if
24	THE COURT: Any followup questions	24	you but if you can start giving me what I'm
25	from the attorneys based on those three	25	going to need to look at over the weekend. I
	Page 235		Page 237
1	Page 235	-	Page 237
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2	questions? MR. SUGGS: Not from me,	1 2	don't know what I'm doing tonight, but and it may be working on other cases. But once you get
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1 REPORTER'S CERTIFICATE	
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