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 11

TRANSCRIPT OF PROCEEDINGS

March 17, 2008 - Pages 1 through 256

BEFORE THE HONORABLE MARK RINDNER
Superior Court Judge

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

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PROCEEDINGS

THE COURT: Please be seated.

We're back on the record in State of Alaska versus Eli Lilly and Company, 3AN-06-5630 Civil. We're on the record outside the presence of the jury. All counsel are present.

Good morning, everybody. I hope you had a nice weekend.

Just a couple of things. We're still waiting for a couple of jurors who aren't here yet. Am I correct that our schedule today is that we're going to take a State witness out of order first --

MR. FIBICH: Lilly witness.

THE COURT: Excuse me. A Lilly witness out of order. And when that witness is concluded, then we'll resume with the deposition testimony?

MR. ALLEN: Yes, sir. And we have an additional video. You had ruled on it previously. We did 12 minutes of David Noesges and we provided it to the Defendants.

THE COURT: Okay.

MR. ALLEN: And so I can get the exact time but I think -- it's my recall -- we have like -- I may miss it by a couple of minutes, an hour and 48 minutes of additional video. We want to admit a few exhibits. And Mary Beth is going to meet with Mr. Borneman this afternoon after trial.

In addition to that, I have pursuant to the Court's instructions of last Wednesday concerning what testimony I'd like to have admitted concerning the percentage of use other than schizophrenia and bipolar. I have the testimony of Denise Torres, which I just handed you at Page 136, Line 6, through 136, Line 15, which I'd like to introduce and for you to reconsider on. We filed a memoranda -- somebody needs to file a motion with it -- concerning our ability to play the excluded portions of Ms. Joey Eski's deposition concerning the lobbying efforts surrounding restrictions on Zyprexa.

THE COURT: Okay. Let me take these all one at a time.

MR. ALLEN: Yes, sir. I don't need to take them up now. I wanted you to --

THE COURT: To the extent we can

get a few things done and get a few issues cleared up in my mind.

Lilly has filed a response to my inquiry regarding the termination of civil penalties. I need something quickly from the State.

MR. ALLEN: I thought --

MR. FIBICH: I think we've about got that ready, Your Honor. We'll have it to you this morning, I think.

THE COURT: Okay. Then I received Lilly's deposition counterdesignations and objections to the Breier deposition. I assume this is just the original that I'm getting or --

MR. LEHNER: I think they'd added about 12 minutes or so. There was some -- there's new stuff that had not been on the previous stuff and I think this is just a supplement if that's what it is. When we looked at it, there was some new stuff added into Dr. Breier that we hadn't seen previously designated.

MR. ALLEN: Well, if there was, it was unintentional because we actually took Dr. Breier down from an hour and 20 minutes down

to 46 minutes and all I did was cut it, but I'm not going to quibble. I know I cut the deposition back --

MR. LEHNER: I know much was cut but there was a couple pieces added. I think you needed a couple counterdesignations.

THE COURT: Well, they've got three counterdesignations and two objections -- probably the way the numbers are grouped, one series there so I'll take a quick look at that. Does Lilly know what its position is on this page 136 of Torres?

MR. LEHNER: Yes, Your Honor. I think we object to -- you've clearly ruled on off-label and I can't see what this is proving. I'm sorry. This was ruled on before. It goes precisely to the issue that you have --

THE COURT: Well, it doesn't. What we've ruled off before is Lilly's efforts to -- what would be unlawfully do things off-label, but off-label use can be used, as I understand it; it just can't be promoted by Lilly. And all this says is what the percentage is of off-label use rather and there's nothing in here that says that Lilly was doing -- promoting off-label. It

merely says that there is an off-label use and there's a percentage estimate of that. And so that's an entirely different issue.

MR. LEHNER: Okay. And I guess I'm having a hard time understanding what issue in the case that is still relevant. Even if it's true, it's a statement, not quibbling with the fact --

THE COURT: I've had significant testimony as to benefits and risks. And benefits would depend on what you're using it for compared to the risks which are going to be the same, I think, regardless of the use. So, to the extent that the benefits and the use is different than bipolar mania and schizophrenia, there's off-label use. I think that that's relevant to assessing --

MR. LEHNER: And I think it goes to the argument that we made last week, and that is there is no claim here that the failure to warn deals with anything that has to do with the benefits of the product. So, whatever the benefits may be with respect to whatever use the product is put to --

THE COURT: But doesn't the jury

have to assess the warning in the context of understanding the benefit --

MR. LEHNER: Well, I think the jury is looking at --

THE COURT: -- and what it's being used for?

MR. LEHNER: I think if you look under the standard again under Shanks, that's not what the jury is going to be asked to do. The jury is going to be asked to do whether or not the label adequately describes the risks associated with the product.

THE COURT: I'm going to allow the jury to be read -- I assume that's what you were planning to do --

MR. ALLEN: Yes, sir.

THE COURT: -- the portion of the deposition of Torres at Page 136, Page 6 through Line -- excuse me -- Page 136, Line 6 through -- inclusive Line 14 --

MR. ALLEN: Line 15.

THE COURT: -- or Line 15. And then I'm going to get a motion to go with the memorandum in support of the motion to allow the testimony of the lobbying efforts, and I assume

I'll get a response from Lilly?
MR. LEHNER: Yes, Your Honor.
THE COURT: Okay. I'll wait for your response, because I don't want to waste anybody's time. And believe it, when Dr. Hopson testified and was asked the very questions that are cited here, I wrote a note with a big asterisk that says "door open," so you've got a little bit of an uphill battle based on the questions that were asked.
MR. LEHNER: We'll put our best people on responding to it, Your Honor.
THE COURT: But I won't rule on that until I get the response.
Are there any other pretrial issues that we need to pick up?
MR. FIBICH: This is really between us, but I don't believe we've gotten our copy of your brief on civil penalties; termination of civil penalties.
MR. LEHNER: The one we filed this morning with the Court?
MR. FIBICH: Right.
MR. LEHNER: I'll make sure you have it if it hasn't been served. It was

probably served this morning. I think that we were just delivering it when --
MR. JAMIESON: That was one of the two I handed to you.
MR. ALLEN: I gave it to Mary Beth.
MR. FIBICH: Your Honor, at the conclusion of testimony on Friday, we admitted into evidence certain documents related to Kinon's deposition. We want to publish those to the jury before Dr. Inzucchi takes the stand.
THE COURT: When the jury comes in, I'll let them know what documents were admitted after they left on Friday and tell them, and you can make your application to publish them.
Anything else we need to talk about before we get going? Then we'll be off record.
(Off record.)
(Jury in.)
THE COURT: Please be seated.
Good afternoon, ladies and gentlemen. Hope you had a nice weekend. We're back on the record and all members of the jury are present. At the conclusion of our trial, ladies and gentlemen, I suggested to you last week that what we were going to do is finish up

with the State's deposition testimony and the State's case would be over. But instead, we need to take one of the defense witnesses out of order. So the plan for today is to take a defense witness who will be testifying live, and then depending on how long it takes to conclude his testimony, then we'll resume with the deposition testimony from the State and the State will finish up its case.
At the conclusion of the day yesterday, after I let you go, the State offered and I admitted some exhibits. And, Mr. Suggs, do you want to now publish --
MR. FIBICH: I'll do it, Your Honor.
THE COURT: Mr. Fibich.
MR. FIBICH: We would ask permission to publish to the jury, AK1215, AK8905, AK4517, AK1213, AK10140, AL4532, AK5522, AK10142, AK10141, and AK10008.
THE COURT: And these were all exhibits used for Dr. --
MR. FIBICH: Kinon.
THE COURT: Those exhibits may be published. All objections previously made to the

exhibits are preserved.
And Mr. Kantra, why don't you call your witness.
MR. KANTRA: Your Honor, Eli Lilly and Company calls Dr. Silvio Inzucchi to the stand.
THE COURT: Doctor, if you could just remain standing there, we'll put you under oath.
Dr. Silvio Inzucchi,
having been duly sworn, testified as follows:
THE CLERK: For the record, please state your first and last name, spelling both.
THE WITNESS: Silvio, S-i-l-v-i-o, Inzucchi, I-n-z-u-c-c-h-i.
THE COURT: Dr. Inzucchi, please be seated.
Mr. Kantra.
DIRECT EXAMINATION
Q. (BY MR. KANTRA) Good morning, Dr. Inzucchi.
A. Good morning.
Q. Can you tell the jury where you live?
A. Sure. I live in Stratford, Connecticut.
Q. And do you have any kids?

A. I have three children.
Q. And how old are they?
A. The oldest is 18. The two younger ones are 15 and 14.
Q. Tell the jury what kind of medicine you practice.
A. I'm an endocrinologist. That is an internal medicine physician who's done subspecialty training in diseases of metabolism. These are diseases that involve hormones or chemical signals through the blood. One of the diseases that we treat, probably about 50 percent of what we do, is related to diabetes.
Q. And how long have you been treating patients with diabetes?
A. Well, ever since my internal medicine residency back in the mid 1980s. I was certified as an endocrinologist to treat solely diabetes patients after my fellowship training, which concluded in 1994.
Q. And roughly how many patients with diabetes would you say you've treated over those years?
A. It's hard to say. Several thousand, I would estimate.

Q. Do any of the patients that you treat with diabetes also have serious mental illness such as schizophrenia or bipolar disorder?
A. They do.
Q. And about what percentage of those patients that you treat with diabetes would have serious mental illness like schizophrenia?
A. Again, that's hard to estimate. Psychiatric diseases are very, very common in people with diabetes and vice versa, but I would estimate that maybe 20 to 30 percent of our patient population has some form of psychiatric condition or mental illness.
Q. About how much of your time as a physician is spent treating patients?
A. I'm on the faculty, so I do a lot of teaching and some research. I would estimate that about 50 to 60 percent of my time is spent with patients both in the outpatient clinics, but also in the hospitals.
Q. And you also mention that you have research interests as well?
A. Yes, I do.
Q. Can you tell the jury the kinds of studies that you do in research?

A. Sure. My main interest has been in the effectiveness of the various oral agents or pills that we use to treat type 2 diabetes. And also one of my main interests nowadays is the so-called cardiovascular complications of diabetes, such as heart attacks and strokes and how diabetes might result in some of these vascular complications.
Q. And in the context of doing that research, do you perform clinical trials?
A. Yes, I do.
Q. And do you also perform epidemiology studies?
A. Yes, I do.
Q. I understand that you're affiliated with the Yale School of Medicine?
A. Yes, that's my employer.
Q. Okay. And as part of that -- as part of the work that you do at Yale, you teach students, I understand from you and as well, you run the fellowship program that helps to give physicians more specialized training in diabetes?
A. Yeah, I'm director of the fellowship program, so I direct the training program whereby physicians who are now trained in internal

medicine, which is a three-year training period after medical school. These would be diseases of the internal organs; the heart, the liver, the kidney, the hormonal organs, as well. They then decide to subspecialize in only the diseases of metabolism. So this would involve thyroid diseases, diabetes, anything that might deal with metabolism or hormonal conditions.
Q. And the other hat that you wear when you're not busy teaching students and seeing patients is you're the director of the Yale Diabetes Center; right?
A. That's correct.
Q. And what kind of diabetes patients do you treat at the Diabetes Center?
A. Well, we tend to focus on the more complicated ones so we'll get referrals from primary-care physicians who are having a difficult time managing the diabetes of an individual patient. So it's a referral practice, so we'll focus in on the patients that are not doing as well as they could. And I would say that it's the broad spectrum of diabetes; type 1, younger individuals, type 2, obviously is going to be the most common form of diabetes that any

endocrinology program sees.
Q. And among those difficult-to-control diabetes patients that you have at the Yale Diabetes Center, are some of those patients those who have schizophrenia or bipolar disorder?
A. Yes, and they're amongst the most challenging ones.
Q. I understand as well that there are a number of other settings in which you see patients who have diabetes and serious mental illness as well?
A. Well, we perform consultations at a major tertiary hospital known as Yale-New Haven Hospital. It's the primary teaching affiliate of Yale University. And affiliated with Yale-New Haven Hospital are two psychiatric facilities. The first is the Yale Psychiatric Hospital, used to be called the Yale Psychiatric Institute, and the Connecticut Mental Health Center. And we'll perform consultations at these locations for specifically diabetes, but also for other hormonal conditions like thyroid disease.
Q. When you say consultations, you mean people -- physicians at these locations seek you out for advice as to how to treat the diabetes in

these patients?
A. That's right. They'll request that we come to the hospital to consult upon a patient specifically to focus in on in this situation, the diabetes.
Q. Now, we heard some testimony last week about an institute here called the Alaska Psychiatric Institute, which is a State-run mental hospital here in Alaska. Do you -- have you done work in Connecticut with any similar institutions?
A. The analogous hospital, I believe, would be what we call CMHC, which is the Connecticut Mental Health Center, which is an independent building, facility, run by the State of Connecticut, but has very tight links to Yale University. Many of our faculty perform their psychiatric services at that institution, and that's one of the institutions where we're called on to see these patients for their -- for their diabetes.
Q. Doctor, where did you earn your medical degree?
A. I was at Harvard Medical School.
Q. And when was that?

A. 1981 through '85.
Q. And you've already told us that you completed your internship and residency at Yale, is that right, afterwards?
A. That's right. I went from Harvard down to Yale, and that's where I conducted my internal medicine internship and residency.
Q. And are you -- did you take any examinations that would qualify you to treat patients with diabetes upon completing your fellowship?
A. Yes.
Q. And how are you -- are you board certified?
A. Yes.
Q. In what area?
A. It's the American Boards of Endocrinology and Metabolism, but that encompasses the treatment of diabetes.
Q. I understand as well that you are a member of the American Diabetes Association?
A. Yes, I am.
Q. And in that capacity, you work with the professional practice committee?
A. Yes. I'm a member of that committee for

the past couple of years.
Q. And that's the committee at the ADA which is responsible for promulgating the standards of medical care for patients with diabetes?
A. Correct. It's a national committee that meets twice annually to set the agenda for each year in terms of putting together the recommendations to all the endocrinologists and all internists and family practitioners about how to manage diabetes. Because there's new information coming down the pike almost on a weekly basis, and we try to incorporate that new information into common-sense recommendations how to treat real patients.
Q. And in that regard as well, do you review the screening guidelines which help physicians understand how they can diagnose diabetes?
A. Sure. The standards of care incorporate both the diagnosis of diabetes, who should we be screening for diabetes. Once people have diabetes, how do you treat them, which medications you use, when to move to insulin. It's quite a complex area, but we're able to

update these so-called standards of care on an annual basis.
Q. I understand, as well, that you are a member of the editorial board of a medical journal which is called Diabetes Care; is that correct?
A. That's right.
Q. And Diabetes Care is the ADA's leading clinical journal on diabetes?
A. Yes. There are two main journals; one is called Diabetes and that's a scientific journal. You'll read a lot about mouse studies and rat studies in that journal. But the one that focuses on treating humans, real people with diabetes is known as Diabetes Care. It's the leading journal -- probably the leading international journal for the management of diabetes.
Q. Do you also do peer review work for that journal as well?
A. Sure. Of course.
Q. Dr. Inzucchi, have you published articles yourself on hyperglycemia and diabetes?
A. I have.
Q. And all told, how many would you say

you've published?
A. It's hard to say how many were in that specific area but I would say that if you include abstract publications, my total publications number more than 200.
Q. And have you written any book chapters in textbooks regarding diabetes or internal medicine that are widely read?
A. I've written them. Whether they're widely read or not, I'm not exactly sure but two major chapters over the past few years.
Q. Okay.
Are you familiar, through your work, with the published literature on mechanistic studies?
A. Yes.
Q. And have your training and experience given you an understanding of diabetes as it is manifested in larger populations as opposed to just individual patients?
A. Yes. I mean, that's one of the more interesting aspects of diabetes is how diabetes is expressed in different populations. There's major differences in terms of ethnicity, gender, other diseases that are associated with diabetes.

It's one of my interests.
Q. And you told us before that you had conducted epidemiology studies. Do you follow the epidemiology literature regarding diabetes?
A. Sure. It's important to -- particularly, if you sit on the practice committee and as a teacher, you want to try to update yourself on the newest information in that regard. So, it's part of the general diabetes literature and we incorporate that as well.
Q. Doctor, have you ever testified as an expert in court before?
A. Well, twice. One over the past five years.
Q. And what kind of a case was that?
A. The most recent one was a patent litigation case about three to four years ago. The one before that was a patient just needed some medical information given at trial.
Q. So two cases?
A. Two cases, but the first one was -- it must be over ten years ago.
Q. Okay. And have you been compensated for the time that you spent working on this litigation you're appearing in today?

A. Yes, I have.
Q. And what is your rate?
A. $450 per hour.
MR. KANTRA: Okay. Your Honor, Lilly would offer Dr. Inzucchi as an expert in the development, diagnosis, treatment and complications of diabetes, as well as in the design, conduct, interpretation and presentation of data from studies relating to diabetes.
THE COURT: Mr. Suggs.
MR. SUGGS: Yes, Your Honor. I have a few questions for voir dire.
THE COURT: Please.
VOIR DIRE EXAMINATION
Q. (BY MR. SUGGS) Good morning, Dr. Inzucchi.
A. Good morning.
Q. I'm Dave Suggs. We've never met before, have we?
A. No.
Q. Okay. Am I correct you're not an epidemiologist, are you, sir?
A. Not a trained epidemiologist, but I use epidemiology in my teachings and my writings and I've conducted epidemiological studies.

Q. You don't typically prescribe Zyprexa, do you, sir?
A. No. That is a -- obviously a psychiatric medication. My prescriptions mainly to patients with hormonal diseases, so medications for diabetes.
Q. You have had patients that you've treated that have been on Zyprexa, though, correct?
A. Absolutely.
Q. Okay. Those patients already have diabetes by the time they get to you?
A. They sometimes might be seen for thyroid disease or pituitary disease so it's difficult exactly what I saw those patients on Zyprexa for, but some of them may have had diabetes, yes.
Q. Do you recall whether you treated any patients for diabetes who were on Zyprexa?
A. Yes, but not everybody with Zyprexa had diabetes.
Q. And did you ever recommend that anyone who you were treating for diabetes who was using Zyprexa be taken off that drug and be given another antipsychotic drug?
A. You know the prescription of psychiatric

medications is obviously a field unto itself, and I've had a healthy respect for trying to get patients with severe mental illness on the right medications so they don't decompensate any further. So I've made it a policy of mine that if someone is referred to me for diabetes, I tend not to recommend any changes in psychiatric medications, as long as it's working. But that's a decision for the psychiatrist. I typically focus on the diabetes and I treat the diabetes.
Q. So your answer is no. You have never taken anyone off Zyprexa that you're treating for diabetes?
A. That's correct.
Q. Okay. Were you aware that Zyprexa has been contraindicated for diabetics --
THE COURT: Mr. Suggs, this is voir dire, not cross-examination.
Q. (BY MR. SUGGS) You've never conducted any clinical trials to assess the risks or benefits of Zyprexa or any other atypical antipsychotic; is that correct?
A. That's correct.
Q. Okay. You've never conducted any original research of any kind to study the

question of whether Zyprexa or any other antipsychotic drug is associated with diabetes; is that correct?
A. Original research, no.
Q. Okay. You've only read the research conducted by others, correct, published in the medical literature?
A. Published in the medical literature.
Q. But you've never done any of that research yourself?
A. That's correct.
Q. Okay. And have you ever published anything in a medical journal or medical textbook which states that Zyprexa is associated with diabetes?
A. I don't recall so. We have written on the area of screening and diagnosis classification of diabetes, and very often these issues are discussed in terms of metabolic diseases and psychiatric patients.
Q. Your expertise is really limited to the treatment of diabetes, its sequelae and other metabolic issues, correct?
A. Correct.
Q. And you prepared a lengthy report in

this case?
A. I did.
Q. And you were deposed by Mr. Fibich and other lawyers?
A. I recall so, yes.
Q. And I presume you spent time preparing to come here for this trial, correct?
MR. KANTRA: Again, Your Honor --
MR. SUGGS: I was getting into how much he's been paid, Your Honor, which was a subject that Mr. Kantra brought up.
THE COURT: Save it for cross-examination.
MR. SUGGS: Okay. Thank you.
THE COURT: I will recognize Dr. Inzucchi as an expert in the development, diagnosis, treatment and complication of diabetes, as well as an expert in the various studies designed -- in the studies regarding diabetes.
MR. SUGGS: Your Honor, we would object to any testimony by Dr. Inzucchi on causality as it relates to diabetes and Zyprexa.
THE COURT: I'll wait to hear the questions.

DIRECT EXAMINATION (continued)

Q. (BY MR. KANTRA) Dr. Inzucchi, what were you asked to do in this particular case?

A. I was asked to look at this question between the -- the association between Zyprexa and the development of diabetes.

Q. And did you prepare a slide that summarizes your opinion that you reached in this particular matter?

A. Yes, I did.

MR. KANTRA: Can we bring up TG116.

Q. (BY MR. KANTRA) And can you tell the jury what your opinion was regarding whether or not Zyprexa causes type 2 diabetes?

A. Sure. So, after reviewing all the data that's been published, my conclusion was Zyprexa does not cause diabetes, and the reason is it doesn't directly lead to any problems with the two major elements of what leads to diabetes. And that would be insulin resistance and also the production of insulin. And we'll talk about those two matters.

Q. And do you hold that opinion to a reasonable degree of medical certainty?

A. Yes, I do.

Q. In forming your opinions, did you draw on your clinical experience in treating patients with diabetes?

A. Yes.

Q. And did you also rely on the published literature regarding diabetes and atypical antipsychotics and typical antipsychotics?

A. Yes, I did.

Q. Did you also review Lilly's submissions to FDA in regards to glucose matters?

A. Yes.

MR. KANTRA: I thought it might be helpful before we begin if -- if I might, Your Honor, we had a flip chart here with some terms on it that I thought might help the jury understand some of the terms we're talking about. With your permission, I'd like to put that up there.

THE COURT: That's fine. Has your -- have your friends seen the flip chart?

MR. KANTRA: I'll show them. It's just three words that we've commonly seen. Diabetes, hyperglycemia and IGT.

Can you see that?

Q. (BY MR. KANTRA) Dr. Inzucchi, if we

could begin with diabetes at the top. I believe you told us that diabetes is an illness where the body does not produce sufficient insulin, correct?

A. Correct.

Q. And how does diabetes differ from hyperglycemia?

A. Well, hyperglycemia is a term that's used to just describe a high blood glucose, and diabetes is an actual disease state that is manifested by a high blood glucose. So they're similar, but they can't be used interchangeably.

Q. Does everyone who has hyperglycemia also have diabetes?

A. No.

Q. And in a normal person, what kind of -- who doesn't have diabetes or even hyperglycemia, what kind of range in terms of changes in blood sugar levels would you expect to see?

A. Well, they can be quite significant. Normal range for blood glucose is somewhere between 70 and up to 100; 100 marks the transition between normal blood glucose as long as you're measuring it fasting and the higher range. But you don't reach diabetes until you

reach 126. So there's obviously a gray zone between what's normal, 70 to 100, and diabetes, which is 126, and that phase is between 100 and 126. In the normal situation during mealtimes, for instance, our blood sugars can climb 20, 30 even 40 points.

I mean, if you put away a big meal, large amount of carbohydrates, cherry pie, Coca-Cola, you could even get your blood sugar up perhaps 40 or 50 points. That's an increase in your blood glucose. Let's say you start at 75, and you eat something with a lot of carbohydrates, your blood sugar at the end of the meal may climb 30 points.

It sounds like a lot but after eating, that's what normal individuals do. What happens in diabetes, though, is the blood sugar stays high and doesn't come down and that, I think, is one of the important distinctions between the normal fluctuations after blood glucose that happens in all of us and diabetes.

THE COURT: Is somebody who has a blood -- fasting blood glucose of between 100 and 126 hyperglycemic?

THE WITNESS: Yes, I would use that

term hyperglycemic. The specific term is something called prediabetes. So that's that gray zone between -- so 70 to 99 is normal; 100 to 125 is prediabetes. And you can use the term hyperglycemia to describe those individuals and certainly diabetes over -- 126 or higher is definitely hyperglycemic.

THE COURT: Do you use the term above 126 or do people talk about hyperglycemia above 126 or do they just talk about diabetes?

THE WITNESS: You know, it really depends on at what time of the day you're measuring it. So even a normal individual can get up to 126 or even higher after eating. Again, if you've had a couple of cups of Coco-Cola and then dessert, your blood sugar can climb even to the 130 or 140 range. So it's very important to distinguish whether you're talking about the fasting state, which would be at least 8 hours, nothing by mouth, or if you're talking about after eating.

THE COURT: Well, let me ask the question differently then: If you're talking about fasting blood glucose, if it's above 126, do people talk about hyperglycemia or do they

just talk about diabetes?

THE WITNESS: Diabetes. You're not wrong in saying you're hyperglycemic but at that point as long as it's measured on two occasions at 126 or higher, then that's what we call diabetes. As long as you're sure the patient is fasting, which is sometimes difficult to know.

Q. (BY MR. KANTRA) Doctor, you've mentioned fasting blood sugar measurements. Is there another way in which blood sugar measurements are evaluated as well?

A. Yes.

Q. What is that?

A. Well, there's something called the random blood glucose test.

Q. What does that mean?

A. Some people call it the casual blood glucose test. I'm not sure how that terminology evolved, but it's random blood sugar means that you're checking the sugar without respect to meal. So you could have eaten five minutes ago, an hour ago, four hours ago, it's just a -- sometimes you don't even know when the patient ate last but it's a random blood glucose test. And you can use either fasting or random blood

glucose to make the diagnosis of diabetes.

Q. Both are accepted measures of diagnosing diabetes?

A. They're accepted but the thresholds or the cut points, you know, the boundaries of what we consider normal is obviously going to be much higher when you're measuring a random blood glucose.

Q. And what is the cutoff point for diabetes when using a random blood glucose?

A. 200.

Q. Okay. Doctor, last week we heard Dr. Wirshing testify here about an analysis that Lilly did back in 2000 that measured something which was called IGT or impaired glucose tolerance, which IGT was used in that particular study. Is impaired glucose tolerance a term with which you're familiar?

A. Yes, of course.

Q. Is that an accepted term within the world of diabetes and those who treat it?

A. Certainly.

Q. Let me ask you about one term that is not up on the chart, but which we'll be talking about later on and that's a term that's called

insulin resistance. Can you tell the jury what that means?

A. So insulin is a hormone made by the organ called the pancreas. It is the major metabolic hormone and it controls not only blood glucose, but fat metabolism, protein metabolism as well. Insulin has to exert its action in the cells of the body; the heart, the muscle, the fat cells, the liver. And the manner in which the body responds to insulin is known as insulin sensitivity. So when we're young and lean and healthy, we're super-sensitive to insulin. Our body needs to make very little insulin to carry out its actions because the cells are very, very sensitive to insulin.

Unfortunately, as we age, if we put on a few pounds, for some reason the body becomes resistant to insulin. So our insulin sensitivity decreases and at a certain point we become what is known as insulin resistant and that means that insulin doesn't work as well. The action of insulin is not as good as it used to be. There's actually nothing wrong with the insulin molecule itself; it's perfectly fine. It's just that the cells of the body are not responding normally to

that hormonal signal.
Q. Does insulin resistance cause diabetes?
A. No. It's part of the process that may lead to diabetes, but it's not the cause of diabetes.
Q. Did you prepare an animation that might help you in further explaining the disease process of diabetes to the jury?
A. Yes, I did.
MR. KANTRA: Mike, can we bring up TG15. Your Honor, this was something that we shared previously with counsel for the State.
THE COURT: Before you -- TG15 is a term that -- referring to an exhibit that has no meaning.
MR. KANTRA: I'm sorry. We're actually not going to be offering this in evidence. It's just an internal reference point for us.
THE COURT: Okay.
Q. (BY MR. KANTRA) We could begin here. Can you tell the jury a little bit about what glucose is and what happens when we consume glucose?
A. Sure. So, glucose is the main energy

source of the body. It's one of the sugars, and it's found in a variety of foods and the most common food where you find these sugars, including glucose, would be carbohydrates or what we call starches. And here's a picture of bread and just a cartoon to remind us that there is sugar in bread. Even though it may not be sweet, our body breaks it down into sugar molecules. Doesn't have to be bread, it could be potatoes. I'll admit it, I had some pancakes today but it's basically the same idea. Next slide.
So, we will eat the bread obviously, it will go into the GI tract. So now it's in the stomach. And that's the acid of the stomach. Sometimes you might get heartburn. That acid is actually a good thing because it's chopping up the carbohydrates into little molecules of sugar.
You can't absorb bread right into the bloodstream. You have to chop it up into little pieces and the sugar will then be absorbed through the intestines, which are connected obviously to the stomach.
Next animation. We can see the sugar now entering the intestines and the whole

goal here is to get that sugar into the bloodstream because it doesn't do us any good in the intestines. It has to be absorbed because the bloodstream carries the glucose, this energy source, to the rest of the body's cells.
Next slide.
And it's going to travel throughout and reach essentially every part of the body; from your heart to your brain, to your liver, all the muscle, the fat, even your fingernails. Everything needs glucose to survive. And interestingly, the liver has a lot of roles in metabolism, but one of the roles in this specific setting is that it's almost like a sponge for glucose. So we will eat more glucose than we need for that specific hour, and our liver will absorb the glucose as a sponge and then release it in small amounts during the course of the day.
If we didn't have that, we need to basically eat continuously to keep our blood glucose normal. So, we have over millions of years of evolution have devised two or three meals per day and we're able to survive. Our glucose level stays relatively stable even though we haven't been eating for several hours because

the liver sops up the glucose and gradually releases it. It's really a terrific system.
Next slide.
So, as mentioned, the glucose will travel to these organs and we've highlighted just three major ones; the brain, the heart and the skeletal muscle. And these organs will need to absorb that glucose inside the cells, the actual individual components of these organs. And the reason for that is not that these organs are trying to get the glucose out of the bloodstream for the purpose of getting it out of the bloodstream, but they need the glucose to survive. So these cells inside these organs will absorb glucose from the bloodstream in order to burn that glucose for energy.
Q. Does your animation also talk about how the body regulates the blood sugar levels once they're absorbed into the bloodstream?
A. I believe so. I think the next slide shows. We talked about the liver, we talked about the stomach. What about the pancreas? The pancreas is always green on these cartoons. It's actually more like a yellowish. It's not truly green. It's always designated like that in

textbooks.
It is a small organ, it actually has the consistency of jelly and its major role is actually the production of the digestive enzymes. So we talked about the acid from the stomach. After the food passes down the intestine, other digestive juices are secreted into the intestine to help break down the food but that's not what I'm interested in. I'm interested in an aspect of the pancreas that are hormonal signals and one of the major ones would be insulin. So this is a digestive organ that has two roles; it helps break down food, but it also produces this chemical signal called insulin that is critically important to regulate blood glucose.
Next slide.
So here's a blow-up of this pancreas. Still green. And it's producing these little hormonal signals called insulin. If we can run that just once again. So insulin is being produced by the pancreas, and is being put out into the bloodstream. And the signal to make that insulin, to make the pancreas produce insulin is glucose. So it's almost like the

pancreas is measuring the blood glucose every second of every day, and finely tuning the amount of insulin being released in order to keep the blood glucose down into a normal range.
Okay. So now we're getting to the cells. So we assume now that the insulin has actually been put out into the bloodstream by the pancreas, and now the insulin is at the cell where it's going to exert its action. And this is, again, quite terrific.
The insulin molecule binds to its receptor. That's how many of these hormones work. This is a lock-and-key kind of analogy that's very helpful when we teach medical students. We talk about the key being insulin, and the lock being the insulin receptor. Insulin will only bind to its insulin receptor.
Insulin will not bind to a thyroid hormone receptor. It won't bind to an estrogen receptor in women. Similarly -- thyroid hormone won't bind to the insulin receptor or it won't bind to the estrogen receptor. Each of these hormones have their own locks, their specially-designed molecules to exert its unique activity.

Let's run that once more and show you that after the binding to the receptor, the purpose of this is to open up these channels that allow glucose to enter the cell.
So without that insulin molecule, sugar will not enter the cell, and two things will happen: The sugar in the bloodstream will obviously build up because the patient is continuing to eat, and more importantly, the sugar won't be able to enter the cell. And the cell will ultimately not have an energy source and will begin to be dysfunctional for that. So you can see how important the pancreas and the production of insulin really is, because this is what actually regulates not only the blood glucose level, but how much of the sugar gets into the cells to be burned for energy.
Now, here we have a situation known as insulin resistance, and this is what we talked about before. Insulin typically works wonderfully well in healthy, lean young people. As we age, unfortunately, and as people perhaps gain a little weight, they become insulin resistant, which means that insulin doesn't work as well. If you like the analogy of the key and

the lock, the key doesn't -- kind of gets stuck in the lock. It doesn't work as well as it should.
Now, the body is very smart. It compensates for this, and what the pancreas does because it has this sensor built into it to determine how the blood glucose is of every second of every day, the pancreas, obviously, can read when the insulin is not working because the blood glucose won't drop normally. And the pancreas compensates. It makes more insulin.
So let's run this animation again. And we have, instead of one insulin molecule binding to one receptor, we have three. This is the pancreas making more insulin. The glucose still enters the cell because that's what a smart body would do. It would simply compensate for this insulin resistance. More insulin, glucose level gets lowered because the sugar, the glucose is entering the cell just like it happened in the insulin-sensitive patient.
Q. Do you have an analogy that might be useful in helping understand this process of compensation that goes on with insulin resistance?

A. The analogy I use with patients is I think we all have relatives who may be a little hard of hearing, and you still can communicate with them, you just have to raise your voice. You might have to increase the volume of your voice to get that message through. So the analogy that I like is -- this is kind of the pancreas shouting at the rest of the body saying, hey, you're not listening to my signal. I'm just going to make more of it and eventually you'll get the message and you'll get the blood glucose down into the normal range.

So when you look at blood glucose levels in normal individuals and then insulin-resistant individuals, they tend not to be that different. The blood sugar, as we mentioned before was 70 to 100. And in insulin resistant individuals it's going to be in that same range. The insulin levels will be higher. I don't mean to say that's a normal situation, but the glucose level stays normal and in most cases, you don't get diabetes.

Q. So do you -- are part of your slides designed to show that process whereby insulin helps to control the blood sugar levels in normal

patients?

A. So, before we start, let's just assume that this yellow bar here is the amount of sugar in our bloodstream. Let's pick a number, 85. That's a nice, normal blood sugar. And the insulin level here is in green, and it's not important what the insulin level is here but let's just assume that it's normal. Normal values will be 5, 6, or 7. This is in the normal situation where there is no food being consumed, so this is the fasting state. Let's see what happens after we eat.

So we eat, the blood sugar begins to go up, the pancreas realizes that and makes more insulin. At a certain point the blood sugar level is going to start to decline.

Next animation.

That's just the sugar that is in the bloodstream now entering the cells. And it's interesting that the insulin level comes down quite quickly because the pancreas, again, is reading the blood sugar and realizes the blood sugar is coming down. It starts to make less and less insulin.

This is a -- it's a beautiful

system, and it's critically important for the blood sugar to maintain in the normal range and for that sugar to get into the cells, and this system works wonderfully well in most individuals.

Now, let's take a look at the insulin-resistant patient.

Again, that would be the person who perhaps has gained weight, is getting a little older, may be physically inactive. These are things that make us insulin resistant. One thing you'll notice is that the blood sugar is normal, still about 85. But, if you remember, the insulin level used to be down here, 5 or 6. In these folks the insulin level may be 10, 12, 13, 14. Why? Well, the insulin level needs to be a little bit higher to keep that blood sugar down into the normal range. Again, the pancreas shouting at the rest of the body. What happens when we eat?

Next animation.

Blood sugar begins to go up, now you'll see that the pancreas is stimulated in an exuberant fashion. You see how high the insulin level gets? But eventually it works. Next.

Blood sugar comes down. Insulin level comes down. This is a finely-tuned system. This is the pancreas that's compensating for a degree of insulin resistance.

Q. And finally, do you have an animation which shows how things look in a patient with diabetes?

A. Yeah.

So here's the pancreas again and not as much insulin is coming out of the pancreas. This is what diabetes is. If it's type 1, so you have a kid who develops severe hyperglycemia, severe diabetes. The pancreas has no insulin whatsoever. Zero insulin. And they're not insulin-resistant, necessarily, it's just that their insulin is gone. There's an immune destruction of the pancreas called the beta cells. The beta cells just disappear, and that's not compatible with life. You can't live without insulin. Insulin goes away and you need to take insulin injections. But that's not actually what we see in type 2 diabetes.

Let's go back once more and show the pancreas again in the diabetic patient.

Oh, here's the animation about the

insulin-resistant individual. We'll show you another animation in just a bit as to what happens in diabetes but I wanted just to remind you about the pancreatic production of insulin in type 2. It's a little bit different than in type 1 because in type 1 there's zero insulin.

In type 2 there is insulin around, it's just less, there's less insulin coming out of that pancreas. And let's take a look at the bars. So a couple of things -- a couple of comments here. Blood sugar is no longer normal, right? A diabetic patient wakes up with a higher blood sugar. Instead of 70 to 100, it's going to be something like 140. If it's severe diabetes, it could be 200, 250 but let's make that it's 140. The insulin level is still about as high as it was in the insulin-resistant patient. You'll notice that this is insufficient insulin because the blood sugar is not normal. This looks like a normal amount of insulin but for this insulin-resistant patient, they need more insulin; they're not able to produce it. What happens after a meal?

Next animation.

The blood sugar goes up and up.

You get a very anemic response from the pancreas. This is a pancreas that can't do it any longer, can't make enough insulin. This is what type 2 diabetes is. It's not just insulin resistance or just insulin deficiency, it's both together. But the aspect to the physiology, the biology that transitions a person from normal blood glucose to a high blood glucose, which is after all what diabetes is, it's all in the pancreas, it's pancreatic deficiency of insulin that can no longer compensate for insulin resistance that leads to the diabetic state.

Q. Doctor, let's talk a little bit about how much diabetes there is in the United States today. How would you describe the rate of diabetes in the United States?

A. It's increasing at an alarming clip.

Q. And over the last 25 years, is it fair to say that the rate of diabetes has approximately tripled?

A. Yes.

Q. And roughly how many patients in the U.S. have diabetes today?

A. Last count there were approximately 20 million patients, individuals with diabetes in

the U.S.

Q. And are all of those patients with diabetes patients who have actually been diagnosed with diabetes?

A. No, unfortunately not.

Q. And what percentage of patients have not been diagnosed with diabetes but actually have it?

A. About one-third of those have not been diagnosed.

Q. And why is it that there is such a high rate of undiagnosed diabetes?

A. Well, it's really a silent disease. It's not a disease that necessarily gives you symptoms. The main symptom of excess blood glucose is actually increased urination and as a result, thirst. So increased urination and thirst is often an early sign of it, but you really have to get the blood glucose up to about 200 before you start urinating excessively. So readings of 126, 140, 150, there's no way you're going to feel that. You can determine it if you happen to have a blood test, but it is a silent disease, similar to blood pressure.

I mean, many of us may have a

little bit of hypertension or high blood pressure and it doesn't give you severe headaches or chest pain until it gets very, very high, so you need to be screened for these conditions to determine whether you have them.

Q. And is there -- in looking at the situation where there is this undiagnosed diabetes and you've described there being a period of time when there's essentially not a tremendous amount of symptoms, what period of time are we talking about that there's not a tremendous emergence of symptoms?

A. Years.

Q. Okay.

A. It could be up to five or ten years. One large study from England taught us that by the time patients were diagnosed, you could backtrack in time. Based on some testing that was done in that study, it could be ten years before someone may actually get the diagnosis of diabetes.

Q. And after -- after they're diagnosed with diabetes, is there a period of time when they can remain asymptomatic?

A. Yeah, I would say another several years.

I mean, another important point is that diabetes is a very variable disease. Some patients may stay with mild diabetes for years and not progress. The general rule is patients do progress. They tend to get worse and worse as they get older. But there is enormous variability in the expression of this disease.

Q. Doctor, you say it takes in your estimation about five to ten years to develop diabetes. Did you bring along a slide to explain the length of time, the process by which diabetes develops?

A. Yes.

MR. KANTRA: Can we bring up TG7?

THE WITNESS: So this is a slide that we -- I probably use this slide in 80 percent of my lectures when I'm teaching residents and other physicians about diabetes because I think it's really illustrative of the process and makes some very, very important points.

If we presume that the diagnosis of diabetes here is made, let's say this year, 2008, there's a lot of biological, physiological changes going on in the five to ten years prior

to the diagnosis.

Here's blood glucose in green, and these represent really schematically the two processes that we talked about on the earlier animations. The amount of insulin that your pancreas is going to crank out, right, that's insulin production, and how well your body responds to that insulin, and that's insulin sensitivity, but we call it insulin resistance here. Those are really the opposite. If you're not sensitive, you're resistant; if you're resistant, you're insensitive. But for purposes of clarity we've decided to label the orange line here insulin resistance. Insulin resistance is getting worse, and of course insulin sensitivity is being reduced.

Q. What does that show with respect to the first five years in the insulin production?

A. You can see that in individuals who develop insulin resistance, again, unfortunately, this is going on in all of us to some degree. I mean, there's a natural development in insulin resistance as we get older, particularly after age 40 to 45. We can combat that by keeping the weight off and exercising but it's interesting

that it happens to all of us, more so if we gain weight, become inactive. So the insulin resistance increases, but as we've talked about before, this is compensated. The pancreas is real smart. It compensates for this insulin resistance by putting out more insulin.

So you'll see in yellow, the insulin production is increased, is augmented, and then the result of that -- those two processes, insulin resistance getting worse and insulin production getting higher, the result is that the blood sugar stays in the normal range. So you don't have diabetes here; you have insulin resistance, but you don't have diabetes.

Now, in this phase between the two dotted lines, this is the onset of some disease process, and what is that disease process? That's the failure of the pancreas to make insulin. So this is the insulin production of the pancreas is now beginning to decrease. We actually don't understand what's going on here. I mean, if you'd like to make a lot of money, try to figure this out. What happens to transition this individual from somebody making plenty of insulin to somebody who is not able to make any

longer the amount of insulin that they should.

Genetics are probably involved to some degree. But we are completely in the dark about what happens here. Most patients don't experience this, but those that do now have a problem. They have insulin resistance, but the pancreas can no longer compensate for that insulin resistance. So it's almost like their body needs more insulin and the pancreas just can't do it. So that's a recipe for an increasing blood glucose.

Q. Why don't we talk a little bit about diabetes risk factors. And from your perspective, what is a risk factor?

A. Well, a risk factor is a characteristic of the patient that increases the risk of developing a disease down the road.

Q. And there's a difference between a risk factor and a cause, isn't there?

A. Of course, yes.

Q. And how would you describe the difference between a risk factor and a cause?

A. Well, a cause is directly responsible for a condition. So in this circumstance, the cause of diabetes is the deficiency of insulin

production from the pancreas. A risk factor might be family history, your body weight, physical inactivity. These things that increase the risk of getting a disease such as diabetes. But they're not the cause of that disease.

Q. In terms of leading to an outcome?

A. Correct.

Q. You mentioned a couple of diabetes risk factors.

MR. KANTRA: Can we pull up TG3.

Q. (BY MR. KANTRA) Is there a slide that you prepared that identifies the risk factors that the American Diabetes Association has identified?

A. Yes.

Q. Okay. And I want to focus your attention specifically on a couple of aspects of this. If you look at the second item on that list there, overweight or obesity --

A. Yeah.

Q. -- how long has overweight or obesity been recognized as a risk factor for diabetes?

A. Ever since I can remember. Certainly when I was in medical school.

Q. As part of your basic medical training?

A. Yeah.

Q. Let's drop down to family history. You mentioned that a minute ago.

A. Yes.

Q. To what extent does family history identify a risk diabetes? What is the risk associated with family history?

A. It's really important. It's estimated that if you have one parent who has diabetes, then your risk is 25 percent; if you have two parents, it's about 50 percent. There's an enormous risk just from the family history and it may be related to those beta cells, that -- these cells in the pancreas that make insulin, the genes that determine how healthy our beta cells are come from our parents.

Q. And one other one I want to focus on are ethnicity. Are there certain ethnic groups that have higher rates of diabetes than others?

A. Yes.

Q. And does that include Native Americans?

A. Yes. Hispanic Americans, African-Americans, Native Americans. Native Alaskans, for instance, are at increased risk of developing diabetes. And, again, these are

obviously genetically-based. There may be some social aspects to diet and body weight, but most of the experts in this area feel that what determines this is really genetic influences on the cells that make insulin. It's only logical.

Q. Dr. Wirshing told us last week that he did not believe that schizophrenia was a risk factor for diabetes. Do you agree with that?

A. I don't agree with that.

Q. Why not?

A. There have been -- certainly, in my experience I see plenty of patients with severe mental illnesses that develop diabetes. And also there are some published reports on this dating back a number of years that seem to suggest that the risk in the group of patients with schizophrenia is increased. The risk of diabetes.

Q. And those published reports predate or come before antipsychotic -- the introduction of antipsychotic medications?

A. Oh, yes. I believe that the initial reports may have been in the 19th century that this association was initially raised.

Q. Based on your clinical experience, how

would you explain this increased risk that you observed in patients with schizophrenia?

A. Well, the common explanation is that, unfortunately, patients with severe mental illness are not always capable of complying with normal healthy lifestyle. Diet, exercise, keeping the weight off. Now, obviously, these patients are mentally ill and they're obviously distracted by what's going on with the psychiatric condition. So it may be the last thing on their mind, which is probably jog a little bit or eating the right foods, so there tends to be greater overweight and obesity in this population. And I think that's the major reason for them to develop a lot of different metabolic conditions.

I often wonder if -- there is a relationship between stress and diabetes. We know that stress, severe stress can alter some of the hormonal signals in the body, and I've always wondered as to whether these patients who are under severe psychological stress, whether that could be a precipitant for diabetes, but that's really conjecture on my part. The main concern has been their lifestyle.

Q. And has the FDA offered any support for schizophrenia being a risk factor for diabetes?
A. Yes, I believe --
Q. How did it do so?
A. I believe that in the package labels or the prescribing guidelines for the currently used antipsychotic medications, I believe that there is an insert under the warnings section that, hey, this is a high-risk group of patients, be careful. These are patients that tend to be overweight. They tend to get more diabetes than other groups. And it's certainly something that needs to be monitored.
Q. Do you believe that the risk of diabetes goes up with the increase in severity of the mental illness? In other words, does the more seriously -- the more serious someone's schizophrenia is, does that mean they're at greater risk of diabetes?
A. I believe that.
Q. And why is that?
A. Well, for the same reasons; the ability to take part in healthy lifestyle, exercise, eating a proper diet. I think that's going to be even more of a problem in those that are more

severely ill, and this whole notion of stress may be even greater in those patients.
Q. How many people have diabetes risk factors?
A. Oh, gosh. You saw the list. Those are very common things. Greater than 45. Having passed that threshold myself, I have a diabetes risk factor. Many of us have family members with diabetes. A lot of us are gaining some weight over the years as we get older. Hypertension is very, very common. It's hard to put a number on that, but I would say the majority of adult Americans have at least one diabetes risk factor.
Q. So a lot of us do?
A. A lot of us.
Q. And if you were to look at any group of ten people, would you be able to determine of those who had risk factors who would go on to develop diabetes?
A. Well, I'd be able to tell you who had the greatest risk, but I couldn't predict who was going to develop diabetes. I mean, diabetes is a very complicated disease. I mean, which beta cells, which pancreases are going to compensate for the insulin resistance is really anyone's

guess.
Q. How does the number of risk factors affect the risk for diabetes?
A. Well, I believe it's cumulative so that the more risk factors you have, the greater the risk. So if you have a person just with age greater than 45, but compare that to somebody with age greater than 45, with a mom with diabetes, maybe overweight, and maybe has high blood pressure. If you were a gambling person, you would put money on the person with the multiple risk factors to get diabetes.
Q. Does having many risk factors mean that the person will develop diabetes?
A. No, nothing but going in and removing the pancreas surgically is guaranteed to give you diabetes. Diabetes is after all a disease of the pancreas, and there is enormous capability to respond to these challenges as insulin resistance. It's not possible to say in an individual patient whether they definitely or will not get diabetes.
Q. Are there people who develop diabetes who don't have any risk factors?
A. Absolutely. We find at least 10 to 15

percent of our patient population, which is -- which is quite a large number, I think, that don't have any signs of insulin resistance at all. What goes on in those patients may be a disease of the beta cell. May be a very severe beta cell deficiency that we still don't understand.
Q. Let's talk a little bit, again, about the risk factor that we talked about on that slide about weight gain, being overweight and diabetes. And, in particular, we've heard testimony here that Zyprexa causes diabetes because it causes weight gain.
And I want to ask you, first, do you agree that Zyprexa causes weight gain?
A. Yes.
Q. And do you agree that because Zyprexa can cause weight gain it, therefore, causes diabetes?
A. No.
Q. And why is that?
A. Well, weight gain is not the cause of diabetes. Weight gain is a risk factor for diabetes. It presents the patient with insulin resistance. Most patients are going to

compensate, and it's not -- it's not logical to say that the weight gain from Zyprexa leads to diabetes because the cause of diabetes is, as we talked about, the deficiency of the pancreas.
Q. About two-thirds of the U.S. population is overweight or obese; is that right?
A. Unfortunately, yes.
Q. And only 7 percent have diabetes?
A. At last count, yes.
Q. Have you reviewed the studies that relate to weight gain and diabetes in patients who take atypical antipsychotics?
A. Yes.
Q. I want to ask you about three of those studies.
MR. KANTRA: And, again, with your permission I want to flip this over --
THE COURT: Sure. Again, has the State had an opportunity to see it?
MR. KANTRA: Sure. Three studies that should be well-known to you.
Q. (BY MR. KANTRA) Dr. Inzucchi, I want to direct your attention to three particular studies. The first being a study by Allison and colleagues from 2001; the second is by Cavazzoni

and colleagues from 2004; and the third is a study which is known as the CATIE study from 2005, and ask you, first, have you reviewed those three?
A. Yes.
Q. Let's talk about the Allison paper first. That was a study that involved about 3500 patients; is that right?
A. Correct.
Q. From clinical trials that Lilly conducted?
A. Yes.
Q. And these were from studies where patients on Zyprexa gained more weight than with other medications?
A. That's right.
Q. Can you describe for the jury what the findings of that study were?
A. Yeah. There were modest, small increases in the blood glucose levels in those patients who were taking Zyprexa compared to some of the drugs, compared to placebo and compared to an older antipsychotic medication known as haloperidol. But compared to other medications that were of the same class, so-called second

generation, there were no changes whatsoever.
Q. Did they have another measure that they looked at to look specifically at the question of diabetes?
A. Yeah. They looked at whether patients were developing diabetes. So again, an increase in your blood glucose. I think in that paper in one group it was three or four milligrams per deciliter. If you're starting off with a blood glucose of 85 and your blood glucose increases by three or four points, it's 88 or 89. It's nowhere near diabetes. So an increase in blood glucose is very different from developing the disease we call diabetes.
Q. What do the analysis that looked at these thresholds for diabetes tell us?
A. No difference between the groups. So there was no greater likelihood of you developing diabetes if you were taking Zyprexa than if you were taking one of the other medications or even placebo.
Q. Let's talk secondly about the Cavazzoni paper which is listed up there. That was a study -- or an analysis that looked at about 5,000 patients, right?

A. Yes.
Q. Involving about 20 different studies?
A. Yes.
Q. And in that particular study there was a finding that weight gain was associated with an increased risk of diabetes; correct?
A. The weight gain was, yes.
Q. And that was across treatments?
A. Yes and that's not surprising since weight gain was -- since weight gain was associated with diabetes risk in a number of other studies.
Q. Was there any comparison as to whether or not patients taking Zyprexa were at significantly greater risk with respect to diabetes than any of the other treatments?
A. Yes. That was the purpose of the study.
Q. What was the finding in that regard?
A. Again, no difference. So, you were just as likely or unlikely to get diabetes across the treatment form. So Zyprexa, other drugs, placebo, et cetera.
Q. And let's talk about the third study that's listed up there. That's the CATIE study. The jury has already heard a fair amount about

that study. That was a long-term study, correct, or longer term? About one and a half years?
A. Yeah, about one and a half years.
Q. And involved about 1500 patients?
A. Correct.
Q. They looked in that study at a variety of different outcomes including weight gain, correct?
A. That's correct.
Q. They found that there was more weight gain in patients treated with Zyprexa than other antipsychotic medications?
A. Consistent with earlier findings, yes.
Q. Did they make any findings in that study as to whether patients developed diabetes in that study?
A. They did.
Q. And what was the finding?
A. Again, no difference, no statistical difference between the groups, whether you took Zyprexa, one of the three or four other antipsychotic medications. There was the same rates of diabetes over that period of observation.
Q. And in -- in the CATIE study was there a

finding that there was an increase in blood glucose levels?
A. Yes.
Q. But that didn't translate into a finding of more patients with diabetes?
A. Yeah, apparently not. There was modest changes in glucose, but, again, increasing glucose is not the same as diabetes. It just means that your glucose is going up.
Q. What do these studies tell you about whether or not Zyprexa-associated weight gain causes diabetes?
A. Well, all three say no.
Q. Doctor, do you agree that diabetes is a serious disease?
A. Absolutely.
Q. And that it has the potential for serious consequences?
A. Yes.
Q. You also believe that not all cases of type 2 diabetes are equally severe; is that right?
A. Correct.
Q. What determines the extent to which complications may develop in patients with

diabetes?
A. That's a really complicated question. To some degree it has to do with how severe the diabetes is. That's only logical. Somebody who has a blood sugar of 127 just into the diabetic range is not going to be as predisposed to the diabetes complications that we fear as somebody with a blood sugar of 300 or 400. But other co-existing diseases also play a role, such as hypertension. So if you have the combination of hypertension and diabetes, your risk is compounded.
If you have smoking, I tell my patients, listen, if you can just quit smoking and don't treat your diabetes, that's probably better than if you treat the diabetes and continue to smoke. I mean, smoking is a major risk factor for a lot of these complications. So that combination, smoking and diabetes, is a super powerful problem for patients' health.
Q. Let me ask you -- I'm sorry. I just want to ask you specifically about patients that you've seen who have serious mental illness, like schizophrenia or bipolar disorder.
From your perspective, how

important is controlling their symptoms that relate to their mental illness to managing or controlling complications of diabetes?
A. It's critical. I mean, you cannot control a chronic disease like diabetes unless you have control of your severe mental illness. I mean, just think about it. How are you going to comply with the complex treatment programs, the medications, perhaps even insulin injections and also the ability to comply with diet recommendations, exercise schedules? I mean, it's just not possible if someone is in a psychiatric crisis, particularly patients with schizophrenia. You can't treat their diabetes until that's under control.
Q. Doctor, I think you told us earlier that as part of forming your opinions in this matter, you reviewed the available published studies in regards to Zyprexa and diabetes?
A. Yes.
Q. Okay. And as you reviewed those studies, were there particular kinds of studies that you gave more weight to?
A. Sure.
Q. And what were they?

A. Well, the ones that we reviewed on the poster. These were so-called randomized clinical trials. This is the gold standard of doing medical research. You're testing a treatment strategy in two groups; one group that is actually getting that active medication, and one group that is getting another treatment to directly compare the effects of those two treatments, or sometimes that second treatment is actually a placebo or a fake medication, if you will, to see if there is an actual effect of this. This is, again, the gold standard way of doing medical research.

Q. And it's the gold standard because it helps to eliminate the possibility of bias, right?

A. Correct. You'd assume that if the randomization, which is the way you assign patients to Group A or Group B or Group 1 or Group 2, is done, essentially, by a flip of the coin. It's a little fancier than that. There are computer programs that do that now. But it's a computerized flip of the coin, essentially.

And you assume that if the patient group is large enough, that at the end of the day

when you fill up those two groups, you're going to have about the same number of patients who are overweight in one group, about the same number of patients with a familiar history of diabetes in both groups, et cetera. So it's the only accepted way to do medical research that's going to lead to a change in practice.

Q. Now, you also mentioned mechanistic studies in addition to the clinical trials.

Can you tell the jury what a mechanistic study is?

A. Sure. These are smaller studies where we're actually looking at the mechanisms of disease. So, instead of having 1,000 patients in these types of studies, there may be only 10 or 15. And we're asking very precise questions about, you know, what actually happens to the insulin level in this patient? What actually happens to the blood glucose in this patient? Very often we'll do specialized physiological tests on these individuals that may take a whole day, so we can actually look very closely at the biology of what's going on with glucose and insulin.

Q. And with respect to diabetes, is there a

particular type of study that's especially useful in evaluating whether a drug might cause diabetes?

A. Yeah. These tests are called the clamp studies, the clamp studies.

Q. And did you bring with you some slides that might help the jury understand these studies?

A. Yep.

MR. KANTRA: Can we bring up TG11?

Q. (BY MR. KANTRA) Would you tell us, first, about the two types of clamp studies that are available?

A. Now, I would first say that this gets a little confusing. And it -- don't feel bad if you don't get it the first time, because it takes us about two or three lectures to get this through to medical students, so --

But let me just review -- these are clamps, and I'll tell you why they call them clamps. These are research tests. These are tough to do. They're expensive to do. You're not going to do these in 100 patients or 1,000 patients. You can do them in small groups of 10, 20, 30, perhaps 40 or 50 patients.

There's two types. One is called the hyperglycemic clamp. That's fancy talk for a high blood sugar clamp. That's basically asking the question: Hey, how well can this person make insulin? The only way to determine that is to give them a lot of glucose and see what happens to their pancreas, how much insulin comes out of that pancreas.

The second test is called the euglycemic clamp. And that's -- that just means a normal sugar. Eu is normal clamp. And that's asking another question: That's saying, hey, how well does this person respond to insulin? We're testing the insulin sensitivity, or the opposite would be insulin resistant of this individual. And in that circumstance, we're not giving glucose to test how much insulin they can make; we're giving insulin to see how far the glucose drops.

Q. Let's look first at the hyperglycemic clamp.

A. So, again, the purpose here is to basically determine how healthy the pancreas is. If you're doing this in a before and after kind of situation, you're trying to see if the drug

that you're giving could be harming the pancreatic production of insulin.

Q. And is there a slide, then, that shows what that would look like?

A. Sure. So, let me just remind you that the amount of sugar that we give in these patients is fixed. We're trying to get the glucose fixed or clamped. That's where the term comes from. We clamp the glucose at a very high range, and then we ask the question: How much insulin can this person make?

So, before we show the animations, again, this is the hyperglycemic clamp. If we didn't do anything to that patient, the blood sugar would just stay normal, and the insulin here in blue would just stay normal. So we just -- it's a boring test. We just measure insulin and glucose for 12 hours. That's what we'd see. We wouldn't want to do that.

Q. And that's before you administer the drug, right?

A. This is before -- you know, not doing anything to the patient. Just fasting the patient and just observing them. What we actually do is we give a lot of glucose. So we

give lots of this sugar. This is done by intravenous infusion, and we clamp the blood glucose at a high range.

Q. When you say "high range," is that up in the range of diabetes?

A. Yes. We put that -- there's various targets, but one target, for instance, might be 180. So we put that into a high range; certainly in the diabetic range.

Now, in the normal situation, let's see what would happen to the insulin. Well, the insulin -- and this is only logical, right? You give a lot of glucose, and a normal pancreas is going to make a lot of insulin. Now, if the pancreas wasn't healthy, if the pancreas was predisposed to diabetes or was a diabetic pancreas, this is what we would see. We would see a poor insulin response.

Q. Did Lilly actually conduct a hyperglycemic clamp study with Zyprexa that looked at this question of whether it would have a direct effect on the pancreas?

A. Yeah.

Q. So it looked before and then after the administration of the drug?

A. That's right.

Q. And what did it find?

A. They gave the drug for several weeks and they asked the question: Does it affect the insulin production? Because, just a reminder, if you're going to get diabetes from a drug, it's going to affect your insulin production. So the line was like this before the drug, and the line was like that after the drug. So, the insulin production was not impaired by Zyprexa. That was important to me, because I wanted to know, hey, does this drug give diabetes? And this is a very important test, the hyperglycemic clamp, to determine: Is this drug affecting the production of insulin.

Q. Let's turn, then, to the second study, the euglycemic clamp study you described a minute ago, and ask you whether you have some slides that help to explain that as well.

A. Yes. So this is, again, the test of insulin sensitivity. We're not giving glucose to see how much insulin they can make; we're giving insulin to see how effective that insulin is. So we give a fixed amount of insulin through an intravenous line, an infusion. Then we -- now,

we can't just let the blood sugar fall because that wouldn't be really good for the patient. They would feel really bad if we let the blood glucose fall. So we do something else. Instead of measuring how low the blood glucose is, we give them glucose and build up the blood sugar back to the baseline level. And the amount of glucose that we have to give them is an indirect reflection of how low the blood glucose would have gone.

Let me show you what we mean. So, again, if we didn't do any test, blood sugar stays normal. Insulin stays normal. But this is a test now. What we're going to do is we're going to give them insulin. So the insulin level is going to go way up there. In the normal situation, if we did that, look what would happen to the glucose. And that wouldn't be good. Patient wouldn't like that. They would never come back for more research studies.

But, seriously, what we actually do is we give them glucose. We kind of fill up the tank, and this amount of glucose that we need to give them is precisely measured. We can measure this down to milligram, and we can determine how

much glucose we need to give this individual that reflects how sensitive to that insulin they were.

Let me show you what would happen in somebody who was insulin resistant. Now, this person, we give them the same amount of insulin and their blood glucose would have dropped, but only perhaps half as much. We still don't want them to do that, because that wouldn't make them feel good. So we fill up the tank and we give them that much glucose. Now, you can see if we did patient A and then patient B, obviously patient A was much more sensitive to glucose because their glucose dropped further and we needed to give them much more glucose to bring them back up to normal.

Patient B is very insulin resistant. This person perhaps is older, maybe more overweight, and that person required very little glucose to bring their glucose level normal. This can be precisely measured and precisely compared.

Q. So if a drug caused insulin resistance, you would be seeing a very small amount of sugar that would be needed; is that right?

A. If it did it directly under the time

frame that we're doing the study, absolutely. I mean, if a drug leads to insulin resistance, this is the way you find -- this is the gold standard way of determining that.

Q. And did Lilly do one of these euglycemic clamp studies to evaluate whether or not Zyprexa caused insulin resistance --

A. They did.

Q. -- acutely?

And what was the finding?

A. No change. So, the amount of insulin sensitivity, whatever it was, it could have been high or low, but it wasn't changed by the medication. It really had more to do with what was the underlying insulin resistance of that patient. My recollection is this was a normal human volunteer study, so these were reasonably insulin-sensitive individuals and there was no effect of the drug, at least as far as the euglycemic clamp was concerned.

Q. Okay. Let's move off of the mechanistic studies for a moment and talk about the other studies that you considered in your review of the literature. I want to touch briefly on the clinical trials.

You've already told us the three that are up on this board up here: The Allison, the Cavazzoni and the CATIE analysis, correct?

A. Yes.

Q. And those studies found no increase in risk of -- no significant increase in the risk of diabetes notwithstanding weight gain, correct?

A. Correct.

Q. Okay. Let me ask you, then, to focus -- after talking about the mechanistic and the clinical trial studies, which you consider most significant, did you also consider studies which are called epidemiologic or observational studies?

A. Yes, I did.

Q. Okay. And those are studies that essentially give us a 35,000-foot look at the data, right?

A. Yes.

Q. And in the context of atypical antipsychotics and diabetes, they are studies that look backwards in time, right?

A. Yeah, that's why they were observational. In other words, things have already occurred and now we're going to look back

at what happened to try to pull out the truth.

Q. And the information from these particular studies come out of databases that are designed for other purposes, right?

A. Yeah, these are huge databases. They have thousands, sometimes tens of thousands of lives encompassed within them. They're often set up to -- a health insurance company may want to track, you know, some financial data on patients, and if they have some interesting information regarding the diagnosis of diabetes, what the heck, you could go back and look at that to see if you can find any correlation -- you can't find causality; you can just find correlations between a drug and a disease.

Q. And these studies have important limitations, right?

A. Hugely important limitations.

Q. And one of those limitations is that unlike in the clinical trials, the groups are not equivalent necessarily in terms of their risk factors, right?

A. Yes. If a person took a medication because they were sicker, for instance, it's going to look like that person does worse with

that medication, but that's because they were sicker at the beginning. You really need to adjust for the severity of the disease, and these databases often don't have the critically important bits of information to properly adjust for those differences.

Q. And this is in contrast to the clinical trials where you could equalize or put together patient groups that have risk factors that are comparable?

A. The computerized flip of the coin does that automatically for you.

Q. Okay. Can you tell us what your overall conclusions were from your review of these epidemiologic or observational studies?

A. Well, I was completely confused. I mean, some studies suggested that all patients who took these drugs were at increased risk of diabetes compared to people not taking these drugs. We already knew that. We know that people with schizophrenia are at increased risk, so comparing them to patients who were taking antibiotics or antidepressants, it's not surprising that you might find an increased risk.

There were some studies clearly

that showed olanzapine-treated patients were diagnosed more with diabetes over time. Clearly, those results are out there. But there are other studies showing that there was no effect, or that another drug might have had a greater effect than olanzapine.

So, it's almost like the more I read, the more confused I got. There were arrows pointing in several different directions. So, you've got to look at the totality of the evidence, the potentially biased observational studies. They're important. I mean, I've done these studies. Don't get me wrong. They're important to raising questions about disease, but they don't show you the truth. You can only know the truth by these gold standard tests, which would be the randomized clinical trials and then supported by the mechanistic studies.

Q. Was one of the observational studies that you reviewed as part of forming your opinion in this case a study that was done by Dr. William Wirshing?

A. Yes.

MR. KANTRA: Mike, can you bring up AK10140? And in particular, can we go to, I

believe, internal page 6.

Q. (BY MR. KANTRA) Doctor, this was -- you understand that Dr. Wirshing was an expert for the State in this matter?

A. That's what I'm told, yes.

Q. And did this study evaluate whether patients developed diabetes while on antipsychotic medications?

A. Yes.

Q. And this is a study that had about 200 patients in it; is that right?

A. Yeah, a little over 200.

Q. And roughly about 30 patients on Zyprexa?

A. Yeah, about 30.

Q. And they looked at patients over a period of about two and a half years?

A. Correct.

Q. And that was longer than the CATIE study; is that right?

A. About a year longer, yeah.

Q. And in terms of the conclusions with respect to whether or not there were significant differences among the treatment groups, including Zyprexa and other medications with respect to

diabetes, what was the conclusion?

A. Well, here, we can read that. This is in yellow now. No statistical differences were found for the percentage of patients with clinically significant changes in glucose levels between groups. Overall, 48 percent of patients getting this drug, clozapine; 25 percent of patients getting Zyprexa, that's olanzapine; 21 percent of patients getting risperidone; and 25 percent of those getting quetiapine developed clinically significant elevations. Here we're talking about --

Q. Cholesterol --

A. -- cholesterol.

MR. KANTRA: If you go up, Mike, just a little bit from there. And if you look at the sentence that says, Using a cutoff of 200.

A. This is an analogous sentence here. Taking the cutoff of 200, and that's because they had random glucose. They don't know if the patients were fasting or not. This is a chart review study. They got about 200 charts and they reviewed the charts, but everything had already occurred. Using the cutoff of 200, 4 percent of patients receiving clozapine; 5 percent receiving

olanzapine, that's Zyprexa; 8 percent of those receiving risperidone; and none of the patients receiving quetiapine developed clinically significant elevations in random glucose.

Q. (BY MR. KANTRA) So the less -- there were fewer elevations on olanzapine than on risperidone in this study?

A. Well, in this study, but, you know, this is such a small study it's really hard to make any conclusions. But they looked, at least, over two years and they couldn't find a difference. This seems to support the conclusions of the randomized clinical trials. But, again, these studies are okay for what they are, but you really need to interpret them very, very cautiously. You can't make any conclusions from them.

Q. Lastly, I want to turn your attention to something which has been referred to as case reports.

A. Yeah.

Q. And case reports are usually a single published study or sometimes a series of patients that are reported in literature?

A. That's right.

Q. And did you review the case reports for Zyprexa?

A. Yes.

Q. And did you reach any conclusions about whether they were sufficient to establish causation?

A. You can't -- you can't prove causation with a case report. This is basically a physician who has seen a patient, who took in this circumstance, Zyprexa. The patient then developed diabetes, and that's about what the association is. There's no way to prove causality. They're interesting. They need to be done. They're most interesting for rare conditions.

Diabetes, as we've talked about, is a really common thing. I mean, million, million and a half new cases per year in this country. These case reports are more notable when the effect is rare. So, you know, your ears turn green; that's really rare for that to happen from the medication. So if we had two or three cases come through that says, hey, this drug leads to green ears, I think everybody would say, whoa, this is something we need to take seriously.

But when a drug is associated with diabetes or high blood pressure, it's really hard to know whether it's a cause-and-effect relationship.

Q. And did you review as part of your analysis of the literature things which are called positive rechallenge cases?

A. Yes.

Q. And those are cases where an individual is placed on the drug, developed an event, went off the drug, the event went away, back on the drug, and the event redeveloped?

A. Yes.

Q. Did those reports change your opinion as to whether or not those kinds of publications would establish causation for Zyprexa?

A. No. I mean, obviously they're more interesting, but there's only a handful of them. You know, diabetes can wax and wane. People are being treated, they're coming off medications, they're losing weight, gaining weight. I mean, there's a lot of things going on with diabetes. I don't think -- certainly in light of what we've just talked about, this is very convincing evidence that there's no risk of increasing

diabetes from the mechanistic, from the clinical trials. They don't change my mind.

Q. And did you also review the spontaneous adverse event reports as well?

A. Yes.

Q. Those are unpublished studies typically that go into FDA?

A. That's right.

Q. And was your opinion in regards to whether or not those established causation the same as with case reports?

A. That's correct.

Q. That they do not?

A. They do not. The problem with these reports is that, you know, no one reports, my patient took Zyprexa and didn't get diabetes. I mean, there's no -- there's no sense of what the denominator is here. It's just that, hey, this is an observation I made. And they're important, they need to be done, particularly for these rare conditions. But for diabetes, I think it's less helpful.

Q. So, in sum, as you look back over all of these studies, the mechanistic studies, the clinical trial studies, the epidemiologic

studies, case reports, spontaneous adverse event reports, what is your overall conclusion as to whether or not Zyprexa causes diabetes?

A. There's no evidence that diabetes is caused by Zyprexa.

Q. Okay. I want to focus your attention on something the jury has heard a lot about, which is the ADA consensus statement regarding diabetes and obesity.

Are you familiar with that?

A. Sure.

Q. And you told us earlier that you were a member of the American Diabetes Association, right?

A. Yes.

Q. And that meant that you -- it didn't mean that -- but you are also a member of the editorial board of Diabetes Care?

A. That's correct.

Q. That's the journal that published this consensus statement?

A. Yes, but I was not on the editorial board when it was published. I just joined last year.

Q. Understood. You've sat on consensus

panels sponsored by the ADA yourself?

A. Yes.

Q. Can you tell us what the purpose of a consensus statement is?

A. Well, it's a group of physicians that are called by a professional organization like the ADA to come together to listen to evidence when there's a controversy in a specific area. When we don't know what to do, when there's lots of data coming at us that is conflicting, where the optimal clinical trial has not yet been done, to try to weigh in on this important clinical question.

Q. Do you consider it to be the final word or binding on physicians?

A. No. There's a lot of arguments about, you know, what role these consensus statements have. They're important. They come from authoritative sources. But they basically make suggestions mainly about what needs to be done. You know, what we know, what we don't know, where do we need to go from here to find out the truth. And we as clinicians need to take the recommendations and interpret them and apply them to our clinical practice. They're not as

important as what we call the standards of care. These are direct from the ADA. You really need to do this or you're providing substandard care.

Q. And are you familiar, as a result of having reviewed this particular consensus statement, with Table 2 in that publication?

A. Yes.

Q. And that's the publication that looks specifically at whether or not there's an increased risk among the various atypical antipsychotic agents?

A. Correct.

Q. And, in particular, I want to ask you whether you agree with the ranking with respect to the risk of diabetes here?

A. I don't.

Q. Why is that?

A. Well, as we've just talked about, when you look at all the evidence -- and I will admit that some of the evidence that we talked about has been accumulated since this consensus statement was published in 2003, 2004. But, again, between the mechanistic studies showing no effect on the pancreas or direct effect on insulin resistance, with the clinical trials

showing no effect on the diagnosis of diabetes, and with the epidemiological studies being somewhat discordant, I don't think that I would have put much of a difference between these medications. I think all these patients are at increased risk of diabetes, and my personal view is that the drug treatment itself may be an insignificant aspect to the diabetes risk.

Q. Let's talk about the labeling with respect to Zyprexa. And, in particular, I want to ask you: As a clinician who treats patients and prescribes medications, are you someone who is familiar with and read medication labels?

A. Yes.

MR. SUGGS: Excuse me, Your Honor, I'm going to object. I don't believe that he was qualified for that by the Court.

MR. KANTRA: We talked about the present -- sorry.

(Bench discussion.)

THE COURT: What does the report say about this?

MR. KANTRA: Very specifically in the report a paragraph where he talks about -- if I can have him read it --

THE COURT: I mean, I'm just saying that --
MR. SUGGS: Honestly, I can't remember. I remember when we were doing the -- it wasn't included --
MR. KANTRA: I'm happy to proffer -- I'm happy to bring the report, have him read the report.
THE COURT: To the extent it was gone into in his report and -- was he deposed on this topic?
MR. KANTRA: Yes, he was.
THE COURT: I'll allow the question.
(End of bench discussion.)
Q. (BY MR. KANTRA) Let me ask you again: As a clinician who prescribes medications, are you familiar with and have you read medication labels?
A. Yes.
Q. And from your perspective, do you believe that there is information that you rely upon in the adverse reaction section in determining the safety profile of a medication?
MR. SUGGS: Objection, Your Honor.

He doesn't prescribe Zyprexa.
MR. KANTRA: That's not my question.
THE COURT: I think this is a general question, not a specific question. So as a general question, I'll allow it.
A. So, I do read the labels and I think the information in the adverse effects section is one area that I always go to early on because as physicians, we're taught, do no harm. That's one of the most important lessons we learn in medicine, and every medication has benefit and always some risk. So we're always focused on what are the adverse events that we might expect with this medication so that we can counsel the patient and make a decision as to whether the risk/benefit ratio is worth it.
Q. (BY MR. KANTRA) And could you describe what you understand the purpose of -- as a practicing physician, again, what the purpose of labeling is?
A. Well, again, it's to inform the prescriber as to what the risk/benefit ratio will be in this specific patient with this specific drug. All medications, as I said, have some

downside, and we need to be very aware of that potential downside and look at the expected benefit compared to the possible risk.
Q. And do you expect that every single data analysis that a company has ever done would be included in labeling?
A. No. I mean, it's -- hopefully it's a distilled version of what's happened in the clinical trials. There's a discussion between the company and the Food & Drug Administration, the FDA, as to what ultimately gets into the label.
Q. And where do you get your information about the labeling for medications?
A. Well, I actually like to read the label itself. Very often we get medication samples and when there's a new drug, I like to update myself. So, I actually pull out the label and read the label. But it's also available in the PDR, the Physicians' Desk Reference. It gets mailed to every physician once a year. They're also available on-line. There are electronic resources. I'm kind of a 1970s kind of guy and I don't use them, but --
Q. There are a number of different ways

that physicians can access labeling?
A. Yeah, Hippocrates. These are downloaded ways to get that kind of information. You can go on-line and download them yourselves. Lectures that we attend, CME, continuing medical education, reading review articles. There's a number of different ways we learn about new drugs.
Q. Have you reviewed the Zyprexa label as part of preparing your expert opinion in this case?
A. Yes, I have.
Q. And did you review the original 1996 label?
A. Yes.
Q. Is it your opinion that the Zyprexa label provided adequate information to alert physicians to a potential risk of diabetes?
MR. SUGGS: I'm going to object, Your Honor. He doesn't prescribe Zyprexa.
MR. KANTRA: I'm asking him as a prescriber of medication whether information about weight gain --
THE COURT: You're asking him specifically about the Zyprexa label that he

doesn't prescribe, correct?
THE WITNESS: That's correct.
MR. KANTRA: Can we approach, Your Honor?
THE COURT: You may.
(Bench discussion.)
THE COURT: Just before we get started, it's Mr. Suggs' witness.
MR. SUGGS: He's whispering in my ear.
MR. KANTRA: Again, from the preparation of his expert opinion in this matter and the report that they had and the deposition that they took in this matter, all of that is in there in regards to his expert opinion with respect to Zyprexa. And the information that we're trying to elicit is as somebody who is familiar with diabetes and its risk factors, whether or not he prescribed Zyprexa, would a physician seeing a label like this understand that there was a risk of diabetes. That's all we're asking him.
MR. SUGGS: Your Honor, from our perspective, you have to weigh the benefits and the risks as to whether a drug's being used. He

doesn't treat psychiatric conditions --
THE COURT: I'll allow the question to be asked for the limited purpose of in his opinion, is the risk of diabetes being -- or the other diseases we're talking about being adequately disclosed, and you can ask all those questions on cross-examination.
MR. SUGGS: Thank you, sir.
(End of bench discussion.)
MR. KANTRA: If we could bring up, Mike, what's been marked as EL 2954A --
THE COURT: Mr. Kantra, we're getting to a point where I probably want to take a morning break when you get to a convenient -- I don't know if this is it or --
MR. KANTRA: We're just about finished. I would say five minutes and we'll be done.
THE COURT: Why don't we finish and take our break then.
Q. (BY MR. KANTRA) Okay. I want to focus you on this particular document here. And if you look at the bottom of that, do you see that label as marked from 1996?
A. Yes.

Q. And is that one of the labels that you reviewed in this particular case?
A. Yeah.
MR. KANTRA: Okay. Mike, if you could turn to internal page 16.
Q. (BY MR. KANTRA) And this section in particular about weight gain there.
Dr. Inzucchi, did you review that information in the weight-gain section?
A. Yes, I did.
Q. Okay. And did that information in the weight-gain section place physicians on notice of a risk of diabetes with Zyprexa?
MR. SUGGS: Objection; calls for conjecture; speculation.
A. Well, it certainly put --
THE COURT: I'll overrule the objection.
A. It certainly made clinicians who were prescribing this drug aware about the weight gain. It was pretty explicit. It mentioned what was seen in the clinical trials down to the amount of weight, the percentage of patients who gained weight, even the percentage of patients who gained a significant amount of weight. Seven

percent of your body weight is just, for some reason, considered a significant amount of weight. So it gave those percentages. So, clearly, individuals who read the label and prescribing this medication would have been informed about what was a well-known side effect of not only this drug but a lot of drugs of this class which is, unfortunately, weight gain.
Q. (BY MR. KANTRA) And my specific question to you is: Does that information on weight gain in the labeling provide sufficient notice to physicians of the risk of diabetes?
A. Well, we know about the connection between weight gain and diabetes. I mean, anybody who has been to medical school knows that. So, yeah, that seems logical.
Q. And was there any other information in the package labeling relating to diabetes that would have put physicians on notice of that risk as well?
A. Well, I believe lower down in the label under -- in the same section their was mention of reports of diabetes occurring in the clinical trials.
Q. Doctor, I want to ask you: Are you

familiar with the 2003 label for Zyprexa? Did you review that as well?
A. Yes, I did.
Q. Okay. And, in particular, did you review the warning in that label?
A. Yes.
Q. Okay. And did that warning regarding diabetes include any conclusions regarding causation?
A. No. My recollection of that label mentioned that this is a high-risk group of patients, patients with severe mental illness, and that monitoring of their blood glucose would be warranted because of that increased risk across the treatments, the strategies for those patients.
Q. And did that label rank the atypical antipsychotics with respect to the risk of diabetes?
A. I don't believe so.
Q. And did the labeling for Zyprexa adequately reflect the risk of diabetes as the data evolved over time from your perspective?
A. Yes.
Q. Let me ask you to summarize just so that

we have clear for the jury what your overall opinion in this case is with respect to whether or not Zyprexa causes type 2 diabetes.
A. That there is no evidence from the studies that I've looked at, looking at all the studies put together, that Zyprexa causes diabetes.
Q. And why do you believe that to be the case?
A. The evidence is not there. I mean, if you believe that connection, you've got to have the evidence, and the best we have is modest changes in blood glucose. There is the weight gain, without question. But the diagnosis of diabetes, there's a bar that you have to reach to be diagnosed as diabetic, and there's no evidence from either the clinical trials -- certainly the mechanistic studies don't inform us as to how this drug could even cause diabetes, and the observational data are all over the map, so I just don't see it.
MR. KANTRA: Thank you, sir. Thank you, Judge.
THE COURT: Ladies and gentlemen of the jury, we're going to take our first morning

break. We'll take about a 15-minute break at this time.
We'll be in recess.
THE CLERK: Please rise.
(Jury out.)
(Break.)
THE COURT: Back on record, please.
THE CLERK: On record.
THE COURT: We're outside the presence of the jury. I've reviewed Lilly's deposition counterdesignations for trial and objections to the few additional portions of the Breier deposition contained at Pages 450 and 451 -- of the deposition of Alan Breier. I'll overrule the objections to the deposition designations of the State. And as to the additional counterdesignations, I find that those do not need to be included in the State's presentation for completeness. They may be included as part of cross-examination or in Lilly's case in chief, if Lilly wishes to include them.
We'll be off record.
THE CLERK: Off record.
(Break.)

THE COURT: We're back on the record. Parties are present, the jury is all present. Mr. Suggs.
MR. SUGGS: Thank you, Your Honor.
CROSS-EXAMINATION
Q. (BY MR. SUGGS) Dr. Inzucchi, you do not prescribe Zyprexa, correct?
A. That's correct.
Q. You would agree that those doctors who do prescribe the drug need to weigh both the risks and the benefits, correct?
A. Absolutely.
Q. Now, you talked about weight gain being in the adverse reactions section, at least in the labeling up until 2007, correct?
A. Yes.
Q. Are you aware that it's in --
MR. KANTRA: Objection, Your Honor. I don't believe he testified to that.
Q. (BY MR. SUGGS) You talked about labeling in 1996 and 2000 and 2003, correct?
A. Yes.
Q. Okay. Are you aware that weight gain is now in the warning section in the 2007 label?
A. Yes, I am.

Q. Okay. Now, the adverse reactions section talked about long-term weight gain being 5.4 kilograms; is that correct?
A. Say that once more, please.
Q. Sure. The adverse reactions section in the label for '96, 2000, 2003 said that long-term weight gain was 5.4 kilograms, correct?
A. I don't recall the specific number, but I'd be happy to look at it.
Q. The jury has seen this before. This is a blow-up of the adverse reactions section and you see that -- oh, here we go. Weight gain, average weight gain during long-term therapy was 5.4 kilograms?
A. Yes.
Q. Okay. Now, 5.4 kilograms works out to about 11.8 pounds or something; is that right?
A. Yes, about that.
Q. And were you aware that Lilly's clinical trials showed that average weight gain in patients who use Zyprexa for a year was 24 pounds?
A. We'd have to look at the specific trial. There are many different trials that have been done and --

Q. Well, my question, sir: Were you informed of that? We've had testimony from Dr. Beasley and others that the average weight gain in one year was 24 pounds. Were you aware of that? Yes or no?
A. Again, I'd have to look at the study result. I don't recall that number specifically.
Q. Okay. So, no, you do not recall that?
A. I don't recall that number specifically.
Q. Okay. You'd agree with me, wouldn't you, sir, that a doctor who's considering using Zyprexa in his patient ought to be aware that the average weight gain over one year was 24 pounds, wouldn't you, sir?
A. All the side effects of any drug would need to be looked at, weighing the risks and the benefits, of course.
Q. You agree a doctor should have that information, correct?
A. A doctor would have to have all the information available to make a prescribing decision, of course.
Q. Is that a yes?
A. A doctor would have to have the risks and the benefits of a specific drug.

Q. Would you agree, sir, yes or no, that a doctor should be aware that an average weight gain of a patient on Zyprexa for a year was 24 pounds?
A. I would need to understand the context of that, because there are individual clinical trials that may give a certain amount of adverse effects, certain amount of weight gain. You need to look at the totality of the experience of a specific drug before it makes it into the label and before it's digested by the prescribing physician.
Q. You can't answer my question yes or no?
A. Again, I'm not sure exactly what you're after. The --
Q. My question, very simple question: Should a doctor, before he prescribes Zyprexa to his patients, be made aware that the average weight gain on the drug for those patients who use it for a year is 24 pounds?
A. If that was a single clinical trial, not necessarily. What the prescribing physician needs to know is what is the overall weight gain in the variety of patients that are prescribed this drug. Again, I would need to know the total

experience of using Zyprexa and the weight gain that would be --
Q. Sir, do you have any basis to dispute that the average weight gain is 24 pounds in one year on the drug?
A. I have no reason to dispute it, no.
Q. Okay. And if a person were to gain 24 pounds in one year, which is caused by -- you do believe that Zyprexa causes weight gain, correct?
A. Yes.
Q. Okay. And if a patient did gain 24 pounds in one year that was caused by Zyprexa, how much would that increase in weight over one year increase that person's risk of getting diabetes?
A. That's impossible to say. It depends on what the baseline weight is and other risk factors.
Q. What's the range?
A. I couldn't give you that number now. It --
Q. Doesn't the American Diabetes Association say that for every pound of weight gain, there's an increase of 4 percent in the risk of diabetes?

A. Those statistics come from general population surveys and to know what the risk is in an individual patient, you need to know a little bit more, such as, what is the baseline weight of that person. That person at a normal body weight, an increase in weight may not necessarily increase a risk of diabetes.
Q. Well, as you testified before, the schizophrenic population tends to be overweight anyway, correct?
A. Tends to.
Q. So the schizophrenic population generally would be on the high end of weight to start with even before they started on Zyprexa, right?
A. As a general population, correct.
Q. Okay. So, let's consider that population, the population of schizophrenics who typically tend to be overweight. And if that population were to gain 24 pounds of weight caused by Zyprexa over one year, wouldn't that increase their risk of diabetes?
A. As an overall population, weight gain increases the risk of diabetes.
Q. Okay. And how much would the 24 pounds

of weight gain increase the risk of population -- pardon me -- increase the risk of diabetes in that population? We've heard estimates from Dr. Brancati that it would be four to five times. Dr. Wirshing has testified to a similar number.
Do you disagree with that, sir?
A. I don't disagree with those statements, but my concern is that the risk of diabetes should be apparent, then, in the clinical trials that have been -- that we discussed this morning, and that's not what we see.
Q. I want to make sure I understand your answer. Your answer was -- you said that you did not disagree with those figures provided by Dr. Brancati and Dr. Wirshing; is that correct?
A. I don't disagree with those figures across the general populations, yes.
Q. Okay. So you would agree that a gain of 24 pounds would increase the risk across the population four to five times, correct?
A. I don't have any reason to dispute those, but I don't know them specifically.
Q. If, in fact, the risk of diabetes is increased by a factor of four to five times by a

weigh gain of 24 pounds, don't you think doctors should have been told that the weight gain with Zyprexa was 24 pounds in one year?
A. The issue was diabetes risk, and the studies that had been conducted showed no increase in the risk of diabetes. That's what the real question is.
Q. Well, I'm asking the question. Don't you think doctors should have been told about that?
A. I really would like to know what the totality of that evidence was. If it's from one specific clinical trial, that may or may not be something that would have made it to the label. It really depends on the overall experience with that drug, not an individual data point from an individual trial.
Q. Now, earlier in your testimony you said that there was no evidence of causation; there's no evidence that Zyprexa causes diabetes.
Did you really mean to say that there was absolutely no evidence?
A. There is evidence of association, but there's no evidence of causation.
Q. Okay. You also talked about the three

studies that you -- the three prospective studies that you were talking about, that you were relying on most heavily were the Allison study, the Cavazzoni study and the CATIE study, correct?
A. Correct.
Q. Okay. Now, the Allison and the Cavazzoni study were both done at a time when they would have been considered by the consensus statement, correct?
A. Well, Cavazzoni was published at around the time of the consensus statement, so I'm not exactly sure. I think it overlapped right around that 2003 period.
Q. Well, Dr. Cavazzoni was a presenter at the consensus statement, was she not?
A. I'm sure he presented his data, yes.
Q. Actually, it's a she.
A. She.
Q. It's Dr. Patrizia Cavazzoni. And you're sure she presented that at the consensus conference?
A. I believe I saw her name as one of the presenters.
Q. Okay. Now, the CATIE study was not conducted prior to the consensus statement,

correct? It was published in 2004?
A. It was being conducted during the consensus, but it was published in 2005, I believe.
Q. Correct. Okay. So the consensus panel would not have been able to consider the CATIE study, correct?
A. Correct.
Q. Okay. What is the metabolic syndrome, sir?
A. Well, it's a controversial topic. It's a term that's used by some to describe a constellation of clinical features in patients that seem to go together. So, very often we have patients who have hypertension who also tend to have slightly high blood glucose levels, also tend to be a little overweight, and there are four or five of these features that have been lumped together by some as the metabolic syndrome.
Q. And don't they also tend to have elevated cholesterol and triglycerides?
A. Yes. Actually, low HDL cholesterol and high triglycerides, but not total cholesterol.
Q. Okay. Low HDL cholesterol is the good

stuff, right, the good cholesterol?
A. Correct.
Q. So they have a lower level of the good cholesterol and they've got a high level of triglycerides, correct?
A. Yes.
Q. Okay. And, sir, the CATIE study concluded that olanzapine had effects consistent with potential development of the metabolic syndrome and was associated with greater increases in glycosylated hemoglobin, total cholesterol and triglycerides after randomization than the other study drugs even after adjustment for the duration of treatment; isn't that correct, sir?
A. That's correct.
Q. And they also concluded, the CATIE study did, that more patients discontinued olanzapine owing to weight gain or metabolic effects, correct?
A. Correct.
Q. In fact, you had 9 percent of the olanzapine patients dropping out because of weight gain and metabolic effects compared to only 1 percent to 4 percent with the other four

drugs, correct?
A. Correct.
Q. Okay. And the study also concluded that olanzapine was associated with greater weight gain and increases in measures of glucose and lipid metabolism, correct?
A. Correct.
Q. And you know Dr. Fred Brancati, the diabetes epidemiologist from Johns Hopkins who testified for the State, do you not?
A. Not personally, no.
Q. Do you know him by reputation?
A. I've seen his name on papers, yes.
Q. You're not an epidemiologist, correct?
A. No.
Q. Are you aware that he's testified to this jury that Zyprexa does cause diabetes and causes it at a greater rate than other antipsychotic drugs?
A. I'm aware of that, yes.
Q. Okay. And I think you also testified that you do treat some patients who are on -- who had been on Zyprexa, correct?
A. Correct.
Q. And some of those would have been

patients who had diabetes, correct?
A. Yes.
Q. And you never took them off Zyprexa or asked them to consider going to another drug, correct?
A. Correct. They're often -- by the time they get to the Diabetes Center, they're often stabilized on their Zyprexa therapy or other drugs, and the last thing we want to do is to upset that cart that might allow them to deteriorate in terms of their psychiatric status.
Q. Were you ever informed by Lilly or anyone else that Zyprexa had been contraindicated for use by diabetics in Japan since 2002?
A. Diabetes is really different in Japan, so I don't think you can compare the diabetes in Japan then --
Q. Sir, my question was what Lilly told you. Did Lilly ever tell you that use of Zyprexa in diabetics was contraindicated in Japan and has been since 2002?
A. I'm aware of more stringent labeling for Zyprexa in Japan. The specific details, I'm not familiar with.
Q. So is it fair to say you were not aware

that Zyprexa was contraindicated for diabetics in Japan?
A. That specific aspect to the label I may not have been aware of, but I know that the label is more stringent in Japan for this specific drug.
Q. So your answer is, no, you were not aware of that, correct?
A. Correct.
Q. Okay. Now, you were showing the jury earlier a PowerPoint of how diabetes develops and you had the curving lines over time and so forth.
Do you remember that?
A. Yes.
Q. Okay. Am I correct that that was based on data from patients whose diabetes developed naturally?
A. Yes. It's based on long-term studies in various groups of patients.
Q. It was not based on patients whose diabetes was drug-induced, correct?
A. Correct. Based on long-term studies of type 2 diabetes.
Q. Okay. And, in fact, you would conceive -- leave Zyprexa aside or any -- leave

all the antipsychotics aside for a second. You would agree that there are some drugs that can, indeed, cause diabetes, correct?
A. There are many drugs that are listed as causes of diabetes, but when you actually look at the data that supports that association, sometimes it's relatively weak.
Q. Well, the strength of the evidence wasn't my question. There are, indeed, drugs that you would acknowledge have been described as causing diabetes, correct?
A. Yes.
Q. And the course of development of the diabetes, the length of time that it takes for the patient to develop diabetes when it's drug-induced is different from and shorter than how it develops over time naturally, correct?
A. As a general rule.
Q. It can occur in weeks, correct?
A. With some drugs it can occur quickly, yes.
Q. Okay. We've talked a little bit about the fact that you've been consulting for Lilly previously. You gave a deposition in this case and you prepared a report for this case, correct?

A. I don't consult for Lilly, no.
Q. You're consulting for them now, are you not?
A. I'm providing expert testimony for the legal firm, yes, but I don't --
Q. Okay. Maybe I was unclear. In the course of doing that, you've given a deposition before that was taken by Mr. Fibich and other lawyers, correct?
A. Yes.
Q. And you prepared a report, correct?
A. Yes, yes.
Q. And about how many hours did you put into all that process?
A. I don't have that number. Several -- several dozen hours.
Q. And how much were you paid for that by Lilly?
A. Overall, I can only tell you the hourly amount, $450 per hour.
Q. Okay. And if we do the math -- well, can you give me just a ballpark estimate of how many thousands of dollars you've been paid?
A. I can't give you that estimate right now. I can calculate it for you at a point -- I

don't have that -- I tend to be about six months behind in my invoices, so I don't have those.
Q. Okay.
MR. SUGGS: Can we turn on the Elmo here?
Q. (BY MR. SUGGS) This was the PowerPoint you showed of the American Diabetes Association Risk Factors; is that correct?
A. Yes.
Q. Bipolar disorder is not on there, is it?
A. No. I don't believe any psychiatric condition is on that list.
Q. And schizophrenia is not on there either, correct?
A. No.
Q. Mr. Kantra made a representation as to what Dr. Wirshing testified to last week, and the record and the jurors' recollection of what Dr. Wirshing testified to will govern what was, in fact, said.
But I'll represent to you that Dr. Wirshing testified last week that there is no evidence showing that the disease of schizophrenia without weight gain is a risk factor for diabetes.

Now, would you agree with that statement?
A. That's actually a very complex statement. I would imagine you would have to have lean individuals with schizophrenia to know what their risk of diabetes was, and I don't think a study has been done looking at that specific group.
Q. Well, in fact, there are many women schizophrenics who are lean, correct?
A. Correct, and probably many men that are lean. But the question is whether that group has been studied long enough to know whether schizophrenia by itself predisposes them to risk of diabetes.
Q. In fact, there is no study that you're aware of showing that schizophrenia by itself without weight gain is a risk factor for diabetes, correct?
A. You can't dissect those two, no, you're incorrect.
Q. There has been no study -- well, let me just ask this question: Can you point to any study demonstrating that even if you control for weight, schizophrenia is an independent risk

factor for diabetes?
A. I don't know if the studies that have been published actually controlled for weight adequately to make that determination, so I would say no.
Q. Okay. You would agree, sir, wouldn't you, that schizophrenics need to be closely monitored for diabetes?
A. All -- schizophrenics with diabetes? I'm sorry?
Q. Well, would you agree, sir, that schizophrenics who are being treated with antipsychotic drugs should be closely monitored for blood glucose?
A. All patients that would have risk factors for diabetes should have periodic assessment of whether they develop diabetes.
Q. And that would include blood monitoring?
A. Based on the ADA recommendations, yes.
Q. Okay. And for how long -- going how far back do you think that patients should have been monitored for blood glucose -- schizophrenic patients taking Zyprexa? Is that just a recent thing, or should that have been done years ago?
A. Well, the -- the package insert, I think

we go back to 1996, mentioned the development of weight gain in the clinical trials.
Q. Sir, there was no warning of the need for blood monitoring in the warning section of the labeling in 1996, was there, sir?
A. That's not what I said. I said that the --
Q. I know. This is my question, now, sir. My question is: The 1996 labeling did not warn about the need for blood monitoring in the warning section, did it, sir?
A. I don't believe that there was any mention of monitoring blood glucose in those patients, no.
Q. It does now, doesn't it, sir?
A. I believe, and we can look at the labels side by side, but I believe that the label -- the current label recommends -- does not recommend a specific monitoring program, but recommends that blood glucose, because of the risks being higher in that population, that should be considered as part of the routine clinical care of those patients.
Q. Sir, the 2007 labeling for Zyprexa recommends that every patient starting on Zyprexa

be monitored for blood glucose, correct?
A. I believe so, yes.
Q. And no other antipsychotic requires or recommends that all patients be monitored, correct?
A. I'm not aware of all those other labels. The risk of diabetes is mentioned in all the labels.
Q. Sir, my question has to do with blood monitoring. The labeling for no other antipsychotic recommends blood monitoring for every patient starting on the drug. That's a fact, isn't it, sir?
A. Of the Zyprexa label?
Q. Yes.
A. Yes.
Q. And it's a fact that no other antipsychotic drug makes that recommendation in their label, correct?
A. I don't know that specifically.
Q. You just don't know one way or the other?
A. I don't know that specific point.
Q. Okay. Sir, it's a fact that weight gain came in the warning in the Zyprexa label in 2007,

correct?
A. No. Weight gain has been in the package label, I believe, since 1996.
THE COURT: His question was in the warning section.
Q. (BY MR. SUGGS) In the warning section.
A. The warning -- the warning section was updated, I believe, earlier than 2007. I believe in 2003.
Q. Sir, the warning section in 2003 did not mention weight gain in the warning section, correct?
A. I'm sorry. The weight gain in 2003 discussed glucose issues. The weight gain -- the movement of weight gain into the precautions or warning section occurred in 2007, you're right.
Q. Okay. I'll tell you what, we'll come back to the warnings at the end of the examination.
I'd like to talk about your view of causation. You take the position that in order to be able to prove that Zyprexa causes diabetes, someone would have to show that the drug led to deterioration of beta cell function, correct?
A. That's part of it, but not -- I don't

think I said that.
Q. Well --
MR. SUGGS: Can you pull up Exhibit EL 2005, Chris, and could you go to page 3 of his report?
And could you blow up the third bullet point that starts off "in order"?
Q. (BY MR. SUGGS) Sir, this is an excerpt from your report that you filed in this case, correct?
A. Yes.
Q. And you stated in your report that in order for olanzapine to be causally related to treatment-emergent diabetes, a deleterious effect on beta cell function should be demonstrated. To my knowledge, this has not been demonstrated in humans, correct?
A. That's correct.
Q. And the beta-cell function that you're talking about are the beta cells in the pancreas, correct?
A. That's correct, yeah.
Q. Okay. But you also testified in your deposition that I don't think -- quote, I don't think we know precisely what leads to beta-cell

dysfunction. This is one of the -- I still think one of the great mysteries of diabetes is what causes the beta cell to fail.
Do you recall testifying to that?
A. Yes.
Q. Okay. And you also testified that, quote, this is a real black box in our field, is what causes the beta cell to fail.
Do you remember giving that testimony?
A. That's correct, yes.
Q. Okay. It kind of sounds like a catch-22 to me, Doctor. According to you, the State of Alaska can only prove that Zyprexa causes diabetes if we can prove that it has a deleterious effect on beta-cell function, and then you testified that -- you also say that no one knows what causes the beta cell to fail.
Isn't that a catch-22, Doctor?
A. I don't agree with that.
Q. Okay. In fact, in your deposition on behalf of Lilly that Mr. Fibich took, you testified that you can't even say that weight gain has been shown to cause a deleterious effect on beta-cell function, correct?

A. It has not been conclusively shown.
Q. Okay. And if that's the case, then mentioning weight gain only in the adverse reactions section of the labeling from 1996 to 2006 wouldn't have given doctors any warning that Zyprexa-induced weight gain leads to diabetes; isn't that right, sir?
A. There's plenty of warning in the adverse events section -- adverse effects section, yes.
Q. Sir, do you know what the CFR, the regulations -- the FDA regulations call for in terms of where warnings shall be?
A. No.
Q. Let me show it to you. The jury has seen this quite a few times. It says: Warnings, referring to the warnings section of the label. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there's reasonable evidence of an association of a serious hazard with a drug and causal relationship need not have been proved.

Do you see that language, sir?
A. Yes.
Q. Were you aware of that requirement before I showed it to you just now?
A. I'm not a regulatory expert, no.
Q. But you were not aware of that requirement, correct?
A. I'm not a regulatory expert, no.
Q. Doctor, your test for causation, that the State must prove that Zyprexa has a direct deleterious effect on beta cells in the pancreas is not what the law requires, is it, Doctor?
A. I believe I said it should be demonstrated.
Q. Do you know what the local test is in this case as to whether or not Zyprexa can cause diabetes?
MR. KANTRA: Objection, Your Honor. We're not offering him as a legal expert.
THE COURT: He's testified already that he's not a regulatory expert and doesn't know that, so --
MR. SUGGS: He's using the term --
Q. (BY MR. SUGGS) Doctor, you've used the word cause in your testimony any number of times,

correct?
A. Yes.
Q. Okay. But you don't know what the law requires in terms of proving causation, correct?
A. Again, I can tell you what it means to a physician, to a scientist, what causality means, but I can't opine on legalistic terminology of what cause is.
Q. And that's exactly what I wanted to bring out. You're talking about your individual perception of what cause is from your perspective, but you're not here to tell the jury what legal cause is, correct?
A. I'm talking about the scientific perspective, not just my own.
Q. Okay. By the way, I think you said that there was an association between Zyprexa and diabetes; is that correct?
A. Some studies have shown an association.
Q. Okay. When did those studies first show an association?
A. I believe in the late 1990s and early 2000s.
Q. Okay. So in the late 1990s and early 2000s, there would have been evidence of an

association of Zyprexa with diabetes, correct?
Isn't that what you just testified to, sir?
MR. KANTRA: Objection; Your Honor.
Q. (BY MR. SUGGS) Well, let me ask you --
MR. KANTRA: He's asking him to interpret --
THE COURT: Let him make his objection.
MR. KANTRA: He's asking him again to interpret this regulation. He's not being offered as a regulatory expert.
THE COURT: That was not the question. I'll overrule that objection.
Q. (BY MR. SUGGS) Sir, diabetes is a serious hazard, is it not?
A. Diabetes is a serious disease, yes.
Q. Okay. And you've just testified that there was scientific evidence of an association with Zyprexa and diabetes as early as the late 1990s, correct?
A. The studies I'm referring to are isolated studies. I would assume -- though, again, I'm not a regulatory expert, I would assume that the purpose of that description is to

look at the totality of the evidence. So, is the evidence of an association reasonable and do we look at the entire clinical picture of what is available from the drug company, what's available in independent studies. So, I wouldn't say that the association found in a study or a series of studies would necessarily meet that bar, but, again, I'm not a regulatory expert.
Q. Are you backing away from your testimony that there was evidence of an association of Zyprexa with diabetes as early as the late 1990s?
A. Again, I'm here to interpret the scientific literature, and in the scientific literature there have been studies demonstrating this association as well as scientific studies demonstrating no association.
Q. Okay. Let's talk about some of those other studies that you talk about.
You talk about clamp studies, correct?
A. Well, these are the mechanistic studies.
Q. Yeah, mechanistic studies. Those were studies that were done by Lilly, were they not?
A. I believe they were funded by Lilly, yeah.

Q. Well, in fact, the lead author was Margaret Sowell, is she not?
A. Yes.
Q. And Margaret Sowell was an employee of Lilly, was she not?
A. Yes.
Q. In fact, weren't all of the other authors on those studies, weren't they also all Lilly employees?
A. No, that's incorrect.
Q. Okay. Which ones weren't?
A. I remember that there are at least one or two that were members of the University of Indiana.
MR. SUGGS: Can you pull up the first Sowell study?
I've had marked for identification, Your Honor, AK10171, which is a copy of an article entitled Hyperglycemic Clamp Assessment of Insulin Secretory Responses in Normal Subjects Treated with Olanzapine, Risperidone or Placebo, the authors being Margaret Sowell -- I'm not even going to try on the second one there -- well, I guess I should -- Nitai Mukhopadhyay, Patrizia Cavazzoni, Sudha Shankar, Helmut Steinberg, Alan

Breier, Charles Beasley, Jr., Jamie Dananberg.
Q. (BY MR. SUGGS) And most of those folks are employees of Eli Lilly, are they not, sir?
A. Most, but not all.
Q. Which ones aren't employees of Lilly?
A. It would appear that Dr. Shankar and Dr. Steinberg are on the faculty -- Indiana University School of Medicine.
Q. Okay. And were you also relying on another study by Sowell and others, which I've marked here as -- for identification as Plaintiff's Exhibit AK10172 -- that was published in -- I guess about a year or so later?
A. Yes.
MR. SUGGS: I've had this marked, Your Honor, for identification as AK10172.
Q. (BY MR. SUGGS) And are these two studies that I've handed you, are they the clamp studies that you're relying on, sir?
A. Correct.
Q. Okay. No other clamp studies you're relying on?
A. There was a follow-up study that was a reanalysis of one of the clamp studies, and the first author, I believe, was Hardy.

Q. And that was a post-hoc analysis, was it not?
A. That's correct, yes.
Q. A post-hoc analysis -- let's just tell the jury what a post-hoc analysis is.
Usually what you try to do with an experiment is you specify the analyses that you're going to do ahead of time, correct?
A. Correct.
Q. Okay. Sometimes people take data that's already been generated and they go back and they reanalyze the data, correct?
A. That's correct, yes.
Q. And that's called a post-hoc analysis?
A. Yep.
Q. Scientists don't like those as much, do they?
A. Not necessarily. It depends on what you're looking at.
Q. Well, scientists tend to be more skeptical of post-hoc analyses that were not specified in advance, correct?
A. Not necessarily, no.
Q. Okay. Are they ever?
A. They can be; they can't be. I mean, it

depends on the study that you're referring to.
Q. And this Hardy that you're talking about, study, was really an -- or a reanalysis of the Sowell data, correct?
A. That's correct.
Q. Okay. I have this marked as AK10174.
Is that the Hardy study you're referring to?
A. Yes.
Q. Okay. And I want to make sure we understand this. Those three studies are the clamp studies that you're relying on, correct?
A. That's correct.
Q. Okay. You haven't relied on any other studies?
A. I've relied on over 100 studies.
Q. You haven't relied on any other clamp studies?
A. As far as I know, no other clamp studies have been performed, at least when I conducted my expert report.
Q. Well, Doctor, in fact, there have been some other clamp studies performed since then, and you're not aware of that?
A. I am since then, yes, but at the time of

my report, these were the cardinal studies that I relied on.
Q. Those other clamp studies contradict those studies, don't they, sir?
A. Which clamp studies are you referring to?
Q. Well, Let's talk about them.
Which ones are you aware of, sir?
A. Well, there was one recently published by Sacher, I believe, is the first author.
Q. Well, let's take these in order.
MR. SUGGS: Can you pull up the Ader study?
I stuck the sticker on the wrong exhibit.
Q. (BY MR. SUGGS) I'm handing you what I've had marked as AK10173. It's an article entitled Metabolic Dysregulation with Atypical Antipsychotics Occurs in the Absence of Underlying Disease, a Placebo-Controlled Study of Olanzapine and Risperidone in Dogs.
Have you reviewed this article before, sir?
A. Yes, I have.
Q. Okay. But you didn't tell the jury

about it, did you, sir?
A. It's a dog study, sir.
MR. SUGGS: Okay. Can you pull up the abstract section? Yeah, that column on the left there, Chris, just blow that whole thing up.
Q. (BY MR. SUGGS) It starts off by saying: Atypical antipsychotics have been linked to weight gain, hyperglycemia and diabetes. We examined the effects of atypical antipsychotics, olanzapine and risperidone, versus placebo on adiposity, insulin sensitivity and pancreatic beta cell compensation.
You see that language, sir?
A. Yes.
Q. They go on to say a couple lines down: Olanzapine resulted in substantial increases in adiposity, increased total body fat, correct?
A. Yes.
Q. Then dropping down, they go on to say: Changes in adiposity with RIS.
That stands for risperidone, correct?
A. Yes.
Q. Were not different from that observed in the placebo group. Only olanzapine -- OLZ, that

stands for olanzapine, correct?
A. Yes.
Q. It says: Only olanzapine resulted in marked hepatic insulin resistance.
You see that?
A. Yes.
Q. And tell the jury what hepatic insulin resistance is.
A. We talked earlier today about inability of insulin to work well in peripheral tissues and you can measure this action in a variety of tissues. One -- the clamp studies that I showed was measuring this insulin resistance in muscle mainly, because that's the main sync to blood glucose. You could also measure it using a different technique at the level of the liver, which is the sponge that absorbs glucose.
Q. And, Doctor, was does the word "induced" mean?
A. To result in or to --
Q. To cause?
A. To lead to, to cause, yes.
Q. Okay. Dropping down it says: Olanzapine-induced, or olanzapine-caused, beta-cell dysfunction was further demonstrated

when beta-cell compensation was compared with a group of animals with adiposity and insulin resistance induced by moderate fat feeding alone.
Do you see that language, sir?
A. Yes.
MR. SUGGS: Can you highlight that language? Apparently he just did.
Q. (BY MR. SUGGS) And it goes on to say: These results may explain the diabetogenic effects of atypical antipsychotics.
Now, what does the word "diabetogenic" mean, sir?
A. To induce, to lead to diabetes.
Q. Okay. So we can translate that in saying these results may explain the diabetes-causing effects of atypical antipsychotics and suggest that beta-cell compensation is under neural control, correct?
A. That's what the sentence says, yes.
Q. Okay. And this was published in 2005, correct?
A. Yes, and the Journal of Diabetes focuses on animal studies. This is not a human study.
Q. Well, we've got another animal study I want to show you, but we're going to get to

humans.
I want to show you what I've had marked as AK10175. This is an article entitled Acute Effects of Atypical Antipsychotics on Whole-Body Insulin Resistance in Rats, Implications for Adverse Metabolic Effects.
And it starts off --
MR. SUGGS: Can you blow up the abstract section, Chris?
Q. (BY MR. SUGGS) And it starts off in the first sentence by saying: It is generally accepted that atypical antipsychotics differ in their risk for diabetic side effects.
You see that?
A. Yes.
Q. By the way, this article is published in 2007, correct?
A. Yes.
Q. And I take it you would disagree with that statement that it is generally accepted that atypical antipsychotics differ in their risks for diabetic side effects; is that correct?
A. Some people hold that view.
Q. You dispute that it's generally accepted?

A. I think there's a lot of controversy in this area.
Q. So you would disagree with Dr. Brancati and Dr. Wirshing and Dr. Gueriguian that it's generally accepted that atypical antipsychotics differ in their risk for diabetic side effects, correct?
A. I believe that many have that opinion, but I don't.
Q. Okay. The consensus statement in 2003 came to the conclusion that there was a differential risk, correct?
A. It did.
Q. And you disagree with that?
A. At this point in time I disagree with that because a lot of data has accumulated since then.
Q. Well, in fact, what we're looking at right here is some data that accumulated since then, correct?
A. In rats.
Q. Okay. We're going to get to humans.
If you can drop down about three lines, there's a sentence that starts off: To investigate.

Do you see where I'm starting?
A. Yes.
Q. To investigate whether antipsychotics can acutely cause metabolic effects before any change in body compensation, we studied the effects of four atypical antipsychotics on whole-body insulin resistance.
Do you see that language, sir?
A. Yes.
Q. So, this study was designed to look at whether or not atypical antipsychotics could cause metabolic effects before there was any weight gain, correct?
A. Correct.
Q. Okay. If you drop down to about six lines from the bottom over towards the right on that abstract, there's a sentence that starts off: Olanzapine. Do you see where I'm talking? I wish I had my light pen.
You're there. You found it.
It says: Olanzapine and clozapine acutely impaired whole-body sensitivity in a dose-dependent manner.
Let's stop right there and talk about that for a second.

Can you explain to the jury what that phrase means, sir?
A. The phrase means that, as I was referring to before, insulin sensitivity is like insulin action, how well you respond to insulin. So these investigators are claiming that these two drugs, the two atypical antipsychotics acutely impair that, so they lead to insulin resistance. And a dose-dependent manner means that if they give more of it, then it would seem to have a worse effect.
Q. And that was a statistically significant finding, was it not?
A. Yes.
Q. The conventional measure of statistical significance is .05, correct?
A. Correct.
Q. And in this case, they found that it was statistically significant to the .001 level, correct?
A. Yes.
Q. That's highly statistically significant? It's not even a close call, correct?
A. In this rat model, correct.
Q. Okay. They go on to say that: Whereas

olanzapine and clozapine acutely impaired whole-body insulin sensitivity in a dose-dependent manner -- by the way, before I get off that phrase. When it says it's a "dose-dependent manner," it means the higher the dose, the greater the effect, correct?
A. Well, not necessarily.
Q. What does the phrase "dose-dependent" mean?
A. It means that the effect is dependent on the dose, but it doesn't necessarily mean that the higher the dose is, the greater the effect. It could be the lower the dose is, the greater the effect. It depends on what you're looking at.
Q. In this case it was the higher the dose, the greater the effect, correct?
A. In this specific case, yes.
Q. Okay. And the jury's heard some testimony about the Bradford-Hill criteria.
You're familiar with those criteria, are you not?
A. To some degree.
Q. And when you've got a dose-dependent situation going on, that is one of the

Bradford-Hill criteria for causation, correct?
A. That's completely incorrect.
Q. Let's go on with what these authors said. They found that olanzapine and clozapine acutely impaired whole-body insulin sensitivity in a dose-dependent manner, whereas ziprasidone and risperidone had no effect.
Do you see that language, sir?
A. Yes.
Q. They go on to say: Clozapine also induced profound insulin resistance after dosing at 10 milligrams per kilogram per day for five days.
And then if we drop down, the last sentence in the abstract says: Olanzapine and clozapine can thus rapidly induce, or cause, marked insulin resistance, which could contribute to the hyperglycemia and ketoacidosis reported for patients receiving those therapies.
You see that language, sir?
A. I see the language, yes.
Q. Okay. I think the jury knows pretty well what hyperglycemia is, but I'm not sure we know what ketoacidosis is. Can you explain that, sir?

A. Ketoacidosis is a complication of type 1 diabetes. It doesn't pertain, generally speaking, to type 2 diabetes. It suggests that there has been an autoimmune destruction of beta cells. So, kids that present with type 1 diabetes often present with DKA or diabetic ketoacidosis. It suggests severe insulin deficiency.
Q. And a severe insulin deficiency which has happened rather rapidly, correct?
A. Not necessarily.
Q. Okay. Can it happen rapidly?
A. It can or it can't.
Q. Okay. There's another study that you said you're aware of. That's the recent article by Sacher and others; is that correct?
A. Yes.
Q. This one was done in humans, right?
A. This was done in humans, yes.
Q. I had marked for identification AK10176. And could you pull up the -- by the way, this is published -- well, this is a 2007 article that is a -- what's called an e-pub. Are you aware of that, sir? Do you know what an e-pub is?
A. Yes.

Q. Okay. Could you tell the jury what an e-pub is?
A. It's a publication on-line, typically a couple of weeks before the ultimate publication, printed journal.
Q. And are you familiar with this journal, Neuropsychopharmacology?
A. No, it is not a diabetes journal, not an endocrinology journal. It's something --
Q. Not something you'd usually read, right?
A. I've read this article. It's not a well-known publication in the diabetes field.
Q. Okay. How did you read the article?
A. I learned of the publication and I looked it up on-line. And I'm not sure if I downloaded it or if someone printed it for me.
Q. Who told you about it?
A. I don't recall.
Q. You looked over at Mr. Kantra. Did he provide it to you?
A. I don't recall if this was something that I found on-line or Dr. -- Mr. Kantra may have allowed me to see the paper. I really don't recall.
Q. It starts off by saying in the abstract:

Atypical antipsychotics have been linked to a higher risk for glucose intolerance and consequentially the development of type 2 diabetes mellitus.

Do you see that language, sir?

A. Yes.

Q. Now, when it says "consequentially," what does that mean there, sir?

A. I believe it means as a consequence.

Q. In other words, it's saying that atypical antipsychotics have been linked to a higher risk for glucose intolerance and therefore cause the development of type 2 diabetes; isn't that what that's saying?

A. That's what the sentence says.

Q. Okay. And you disagree with that?

A. Well, I don't disagree that they've been linked. As we said before, there's been associations, but I don't think that the association is valid, nor do I think that the association is causal.

Q. Okay. So you would disagree with their conclusion that it's a causal relationship, correct?

A. Yes.

Q. Okay. They go on to say in the third line down: Using the standardized hyperinsulemic euglycemic clamp technique.

That's the same technique that was used by Dr. Sowell at Lilly, right?

A. Yes, but there's an important difference.

Q. It goes on to say: We compared whole-body insulin sensitivity of 29 healthy male volunteers after oral intake of either olanzapine 10 milligrams per day, or ziprasidone, 80 milligrams per day for ten days.

By the way, those are standard clinical doses for both of those drugs; isn't that correct?

A. Yes.

Q. Okay. So the fact that ziprasidone is 80 milligrams a day doesn't mean that it's eight times more than the standard dose for olanzapine, right?

A. I believe those are considered psychiatrically equipotent.

Q. Okay. So, pharmacologically they're equivalent, or equipotent to use your word

A. You'd have to ask a pharmacologist that question.

Q. Okay. They go on to say that: A significant decrease, with a P value being .001 in whole-body insulin sensitivity from 5.7 milliliters per hour per kilogram after oral take of olanzapine for ten days was observed. The ziprasidone group did not show any significant difference after ten days of oral intake. Our main finding demonstrates that oral administration of olanzapine but not ziprasidone leads to a decrease in whole-body insulin sensitivity in response to a hyperinsulemic euglycemic challenge, correct?

A. That statement is actually incorrect.

Q. That's what the sentence states, correct?

A. The sentence states that, but the sentence is incorrect.

Q. You disagree with the findings of these authors, correct?

A. Yes, I do.

MR. SUGGS: Okay. Chris, could you pull up page 5, please? Go down to the discussion, and can you blow up the discussion -- there you go.

Q. (BY MR. SUGGS) Okay. The discussion starts off by saying: This study is the first to demonstrate consistent in vivo evidence in humans that olanzapine causes significant acute insulin resistance.

Do you see that language, sir?

A. I see the language.

Q. Now, the word -- or that phrase "in vivo," that means what? What does that mean?

A. In living organisms.

Q. Okay. They go on to say: In contrast to previous reports, Sowell, et al., referring to the Lilly studies, our clamp experiments show that there is a significant decrease with a P value of .001 in whole-body insulin sensitivity in response to hyperinsulemic euglycemic challenge in healthy subjects following oral intake of 10 milligrams per day olanzapine. Whereas Sowell, et al., reported an increased total insulin response for olanzapine, they attributed those changes to the antipsychotic-induced weight gain and concluded that the observed changes were insignificant.

Do you see that language, sir?

A. Yes.

Q. And, in fact, the clamp studies that were done by Sowell, they were what, less than three weeks, right?
A. I believe three or four weeks, yes.
Q. And they were done in healthy human volunteers, right?
A. As these studies are usually done, yes.
Q. And they found significant weight gain in those volunteers even in that short period of time, correct?
A. A small amount of weight gain, yeah.
Q. Okay. It was statistically significant weight gain, wasn't it, sir?
A. But modest.
Q. Yes, it was statistically significant?
A. Perhaps not clinically significant.
Q. Can I get an answer to my question? Was it statistically significant?
A. The P value was less than .05.
Q. Thank you, sir.
And, sir, these authors, they described the data from the Lilly folks as being controversial.
Do you recall that?
A. If you point me to the section, I

will --
Q. Sure.
MR. SUGGS: Can you go to page 6, Chris? In the right-hand column, the second full paragraph, the one that starts off nevertheless -- well, let me backtrack from that.
Chris, can you blow up the paragraph ahead of that first?
Q. (BY MR. SUGGS) And about the middle of the paragraph they start off -- or a third of the way down, rather, they say: Our results are consistent with rodent data -- referring to the Hausknecht article and some others -- as well as similar observations in humans. Our current results confirm the previously observed olanzapine-induced changes and glucose metabolism in patients with schizophrenia for healthy volunteers. The time for these metabolic changes to develop in healthy subjects was 10 days of oral intake only, a time period that is shorter than what has been demonstrated for humans before.
Do you see that language, sir?
A. Yes.
Q. Okay. And do you disagree with their

statements, sir?
A. Their conclusions are completely invalid.
Q. Okay. They go on to say in the next paragraph -- they talk about the Sowell data, right? And the data from the Lilly studies, correct?
A. Yes.
Q. Now, in the world of academic publications, in medical journals, to call someone's data controversial is not a compliment, correct?
A. It's not a criticism nor a compliment. It just states that there is some controversy about the data.
Q. Well, in fact, the thrust of this article is that -- and the statement of these authors is that Sowell and the other Lilly authors are standing out there alone in this area, correct?
A. No, that's incorrect.
Q. Well, let's look at what the language says.
By the way, you say you disagree with the findings of these authors and it's

totally incorrect. This is a peer-reviewed journal, is it not, sir?
A. It's a psychiatric journal. It's not a metabolic or a diabetes journal.
Q. Sir, maybe you didn't hear my question.
My question was: This is a peer-reviewed journal, is it not, sir.
A. It's a peer-reviewed psychiatric journal.
Q. Thank you. Are you casting some aspersions on psychiatric journals?
A. When they publish metabolic studies, yes.
Q. Are you saying that the doctors who did the peer review on this article and found it worthy of publication didn't know what they were doing?
A. I would need to know who those physicians were and whether they had a metabolic background.
Q. How can you criticize them if you don't know who they are, sir?
A. Because the study has major methodological flaws and their conclusions are completely invalid.

Q. Let's look at what they said about the Lilly studies. They start off by saying: Nevertheless, it has to be noted that one group has collected controversial data regarding the hypothesis that olanzapine might impair insulin sensitivity in healthy volunteers. Sowell, et al., performed hyperglycemic clamps in healthy subjects before and after three weeks of oral intake of olanzapine, risperidone or placebo. Despite their finding of substantial weight gain that was reported for olanzapine and risperidone, they did not find the observed changes in whole body insulin sensitivity to be significant. The authors attributed the detected increase in total insulin response for the olanzapine group to the antipsychotic weight gain. But in this study no absolute values of glucose infusion at baseline were reported, which makes it difficult to interpret the results.

Do you see that language, sir?

A. Yes.

Q. They are being -- they are criticizing the Sowell study, are they not?

A. Not criticizing the study. They're just point out an exclusion of one data point that

they would have liked to have seen.

Q. They go on to say in the following paragraph: In another study -- again, referring to a study done by Sowell and the Lilly folks, correct?

A. Yes.

Q. -- the euglycemic clamp technique, this group failed -- strike that.

Says: In another study using the euglycemic clamp technique, this group failed to detect a significant difference in whole body insulin sensitivity. This is surprising, but could be partly explained by the partial caloric restriction applied to subjects and by more specific changes in insulin sensitivity of muscle or liver that may have occurred, but were masked because the specific insulin effects were not assessed as hypothesized in Bergman's detailed review on the Sowell studies.

Do you see that language, sir?

A. Yes.

Q. And have you reviewed that Bergman article that has what they refer to as a detailed review of the Sowell articles?

A. I believe so, yes.

Q. Okay. Now, sir, just to wrap up this discussion of clamp studies, none of these clamp studies, whether it's the ones by Sowell or the later ones that contradict Sowell, none of them address the issue of whether chronic treatment with Zyprexa, especially when accompanied by substantial weight gain, has detrimental metabolic effects, correct?

A. Correct. That's impossible to do with these studies.

Q. I mean, that's just the nature of the studies. They can't even look at the issue of whether chronic treatment with the drug resulting in substantial weight gain increases diabetes, correct?

A. But the signal would be perceived in these short-term studies.

Q. Okay. Well, then, according to the studies that we saw in the rat and the dog and the one in humans by Sacher just recently, there was a signal seen, correct?

A. The Sacher study is completely invalid because of its methodology.

Q. I'd like to talk a bit about weight gain, Doctor. In your deposition you told

Mr. Fibich that you couldn't even say that weight gain leads to beta-cell dysfunction, correct?

A. That's not well worked out.

Q. Okay. And under your mindset and the way you look at things, in order to show that something causes diabetes, you need to show that that something has a direct impact on beta-cell function, correct?

A. The issue of causality can be demonstrated through clinical trials as well. The mechanistic studies would lend support to that. So it's not that it must show that, but it would be nice to be able to confirm what you see in the clinical trials with the mechanistic studies.

Q. And, sir, when you're not testifying for Lilly, you know and you tell people that weight gain is one of the contributing factors which causes diabetes; isn't that right?

A. It's clearly a risk factor for diabetes, yes.

Q. Okay. And when something is a risk factor, that means that if you expose a population to that risk factor, that at the end of the day there will be an increased incidence

of people in that population subjected to the risk factor who have the disease, correct?
A. Across a population, yes.
Q. Okay. So, for example, if we're talking about the population of Alaska and the population of mentally ill people in Alaska who are exposed to Zyprexa, you would -- strike that.
If you expose people in the population of Alaska to a drug which causes them to gain weight, that would be subjecting them to a risk factor for diabetes, correct?
A. I don't think that's an accurate statement, no.
Q. Okay. We'll come back to that.
MR. SUGGS: Could you pull up the Inzucchi and Amatruda article?
Q. (BY MR. SUGGS) This is an editorial that you wrote in the journal called Diabetes; isn't that right?
A. No.
Q. What did I get wrong?
A. Diabetes Care.
Q. Diabetes Care. That's the journal of the American Diabetes Association?
A. Yes. One of them, uh-huh.

Q. Okay. And this was published in 2003, correct?
A. Yes.
Q. You've got this great quote at the beginning.
Can you blow that up?
With fat, diabetes begins. From fat, diabetics die, formerly of coma and recently of arteriosclerosis.
Do you see that language, sir?
A. Yes, I do.
Q. And you stand by that, don't you?
A. It's not my quote.
Q. Well, I grant you you didn't -- you didn't say it. That was actually a quote from Dr. Elliot Joslin 75 years ago, correct?
A. That's right.
Q. Okay. You quoted it with approval in an article that you wrote in 2003, correct?
A. This article is about lipids, which is a type of fat and the reference is to the effects of lipid fats in the bloodstream and their relationship to cardiovascular disease, which is well known.
Q. Okay. And what does the phrase "due to"

mean, Doctor?
A. If you give me the context.
Q. Well, just -- if I said that your flight back home was canceled due to weather, what would that mean?
A. Because of.
Q. Yeah, okay. So the factor that -- well, strike that.
MR. SUGGS: Could you blow up the quote of the sentence that says, Chris, With diabetes increasing worldwide due to decreased physical activity and an aging and more obese population?
Q. (BY MR. SUGGS) What you're saying there when you wrote that was that the obesity is -- pardon me -- that the diabetes increasing worldwide is due to decreased physical activity, aging and a more obese population, correct?
A. Correct.
Q. Obesity is clearly a risk factor for diabetes, correct?
A. Obesity is a risk factor for diabetes, yes.
Q. Okay. And if you do something to make a population more obese, you would expect that that

population would have an increased incidence of diabetes down the road, correct?
A. Across the population, yes.
Q. Okay. And in that circumstance you would say that obesity was one of the contributing factors in the increased incidence of diabetes, correct?
A. It's a risk factor for diabetes, yes, of course.
Q. Okay. So, of course, in that situation, the obesity would be a contributing factor in the increased incidence of diabetes, correct?
A. I'm not sure we could use that phrase -- contributing factor really probably boils down to an individual patient. This is a risk factor, and I think that language is a little bit more accurate when you're talking about population risk.
Q. Well, that's what we're talking about in this case, sir, is population risk.
A. And it's a risk factor.
Q. Okay. And if you expose a population to a risk factor, that is going to cause some people in that population to have the disease? You may not be able to predict which ones, but you would

agree that exposure to a risk factor causes people in that population to develop the disease, correct?
A. I think that's inaccurate.
Q. What's inaccurate about it, sir?
A. The cause.
MR. SUGGS: Chris, could you pull up page 2 of Dr. Inzucchi's report? And could you blow up the -- that's it.
Q. (BY MR. SUGGS) This is a bullet point from your report that states: Many risk factors have been identified that predispose to type 2 diabetes. The presence of a risk factor, such as obesity, however, simply increases one's chances of acquiring this disease.
You see that language, sir?
A. Yes.
Q. And when you say that the presence of a risk factor simply increases one's chances of acquiring this disease, you're really referring to the chances of one particular person acquiring the disease, correct?
A. Risk factors can be applied to populations and also to individuals, yes.
Q. And if you step back from the individual

and look at the population exposed to a risk factor, if something really is a risk factor, then it is virtually certain that the population exposed to that risk factor will have an increased number of people with the disease down the road, correct?
A. That's what a risk factor is, yes.
Q. Okay. And metabolic syndrome is a known risk factor for diabetes, correct?
A. Well, it's not as widely accepted as some of the other ones that we've discussed today, because it's really a compilation of many of the risk factors, so the critics of the term metabolic syndrome would say that it doesn't add anything to the equation. It just compiles those risk factors that we already knew about.
Q. Didn't you say in your deposition testimony that metabolic syndrome is a known risk factor for diabetes?
A. I may have. I'm clarifying that metabolic syndrome is not an accepted risk factor as far as the American Diabetes Association list of risk factors is a concern, because the components of the metabolic syndrome are already in the table.

Q. But in your view, and you've testified in your deposition, that metabolic syndrome is a known risk factor for diabetes, correct?
A. Yes, yes.
Q. Okay. So if you have more people with metabolic syndrome downstream, you would expect more cases of diabetes, correct?
A. That's what a risk factor is, yes.
Q. And the CATIE study found that more people with olanzapine -- strike that.
People who used olanzapine had a higher incidence of metabolic syndrome, correct?
A. That's what the paper showed, yes.
MR. SUGGS: Okay. Could you pull up page 3 of Mr. -- pardon me -- Dr. Inzucchi's report.
Q. (BY MR. SUGGS) And Chris is blowing up the bullet point that says: Olanzapine is a powerful and effective atypical antipsychotic medication. One of its side effects, as with many drugs of this class, is weight gain. Most, but not all, processes that increase body weight will, across populations, increase the risk of diabetes.
So you see that language, sir?

A. Yes.
Q. And you're not aware of any evidence or any studies you can point to that show that the weight gain caused by diabetes -- pardon me, strike that.
You are not aware of any studies showing that the weight gain caused by Zyprexa does not increase the risk of diabetes, correct?
A. There were a couple of negatives in that sentence and I lost the train.
Q. Okay. Let me see if I can -- I apologize.
The second sentence in your -- in that bullet point says: Most, but not all processes that increase body weight, will, across populations, increase the risk of diabetes.
Do you see that language, sir?
A. Yes.
Q. Now, Zyprexa-induced weight gain is a process, is it not?
A. Yes.
Q. And you're not aware of any evidence indicating that that process does not increase the risk of diabetes, correct?
A. I am aware of such data.

Q. Okay. What data is it that you're relying on? The stuff that you previously testified before? The Cavazzoni study?
A. The CATIE study, I think, is a good example, the Cavazzoni study. This is a drug that was associated with weight gain in these studies, but when you looked for what we're talking about, which is diabetes, that wasn't seen. So that's an example of a study or two studies where that connection was not demonstrated.
Q. Well, in fact, as we talked about before, the CATIE study found that olanzapine had effects consistent with the potential development of the metabolic syndrome and was associated with greater increases in glycosylated hemoglobin, total cholesterol and triglycerides after randomization, correct?
A. Yes.
Q. Okay. And the CATIE study also found that more patients discontinued olanzapine owing to weight gain or metabolic effects, correct?
A. Yes, but your question was about diabetes.
Q. Well, and you testified that obesity and

weight gain increases the risk of diabetes, correct?
A. The question was about olanzapine and diabetes.
Q. Right now my question is about obesity and weight gain. Obesity and weight gain increase the risk of diabetes, correct?
A. That's what a risk factor is, yes.
Q. And Zyprexa causes weight gain, does it not, sir?
A. Zyprexa does cause weight gain.
Q. Okay.
MR. SUGGS: Chris, can you pull up AK6128, and go to the second page, please. And can you blow up that paragraph -- there you go.
This is an e-mail from Dr. Beasley --
Mark, can you turn down the lights? Maybe it will make it easier to see that.
Q. (BY MR. SUGGS) This is Exhibit 6128 which is admitted in evidence, has been published to the jury before. It's an e-mail from Charles Beasley on March 15, 2001 in which he says, starting about the third line down: One thing we can say definitively is that olanzapine causes

weight gain and for approximately 50 percent of patients in trials who remained on the drug for more than six months, the amount of gain was greater than 10 pounds. Some patients in clinical trials gained as much as 80-plus pounds.
Do you see that language, sir?
A. Yes.
Q. Were you aware that patients in the Lilly clinical studies, some of them, gained more than 80 pounds on the drug?
A. Yes.
Q. Okay. He goes on to say: Lacking empirical data to the contrary, it would be ludicrous to state that such a patient is not at long-term increased cardiac risk relative to prior to gaining that weight, especially if in temporal association with that weight gain the patient developed an increase in fasting glucose and lipid levels.
Do you see that language, sir?
A. Yes.
Q. That would be a fair statement, isn't it, sir? It would be ludicrous?
A. I would not have used that language.
Q. You would agree with it?

A. No.
Q. You disagree with Dr. Beasley who said it would be ludicrous to argue that such patient is not at increased risk of cardiac problems?
A. It would need to be looked at. I would not use the terminology ludicrous.
MR. SUGGS: Chris, can you pull up Exhibit 1453, please?
Q. (BY MR. SUGGS) By the way, had you seen that other document before, sir?
A. These internal Lilly documents?
Q. Right.
A. No, I've not seen anything but submissions to the FDA. Publicly available information.
Q. Fair to say that you simply cannot testify as to what Lilly knew and when they knew it, correct?
A. I've not seen these documents.
Q. Okay. If I could direct your attention to -- by the way, let me represent to you, sir, we've had a lot of testimony about representatives of Eli Lilly meeting with endocrinologist specialists in Atlanta in 2000 to discuss Zyprexa and weight gain and the risk of

diabetes. Are you familiar with that meeting that occurred down there?
A. I did not participate in that meeting.
Q. Is the first you've heard of it when I told you just now, or had you heard of it before?
A. I've heard of meetings. I don't recall specific meetings. Atlanta, I'd heard that there were advisory boards as I would expect there to be with any drug that might have metabolic implications.
Q. Who told you about that? Was it Mr. Kantra?
A. I don't recall that.
Q. Was it one of the lawyers?
A. I believe it was one of the lawyers. I don't have any information about this specific meeting.
Q. They didn't show you any documents?
A. I don't believe I saw any documents other than was specifically submitted at a public forum to the FDA.
Q. Okay. So the only documents that you have seen are either published medical articles or documents which Lilly's corporate folks prepared for submission to FDA, correct?

A. That was -- what I was asked to do was to submit my opinion based on what was the publicly available information, published literature, the scientific literature, yes.
Q. Lilly engages in the process of science, do they not?
A. Yes.
Q. They're supposed to. And Lilly chooses what it decides to publish and what it chooses not to publish, correct?
A. At this point in time all studies that are conducted by pharmaceutical studies are actually publicly accessible, I believe.
Q. Were they publicly accessible back in 2000, Doctor?
A. I don't know when that started.
Q. That didn't happen until?
A. I don't know when it started. I know it's the case now.
Q. Let's talk about the internal data and see if you were aware of that.
MR. SUGGS: Could you go to the second page, Chris. And blow up that e-mail from Charles Beasley.
Q. (BY MR. SUGGS) Actually, I'll represent

to you, sir, this is an October 10, 2000 e-mail from Charles Beasley to Alan Breier, Robert Baker, Paul Berg, Scott Clark, John H. Holcombe, Roland Powell, Alvin Rampey, Roy N. Tamura.
Do you know any of those people?
A. I have met Dr. Holcombe in the past, in the distant past, but not the others.
Q. Dr. Holcombe is an endocrinologist, correct?
A. I believe a pediatric endocrinologist, yes.
Q. He's one of the few endocrinologists working on the Zyprexa project; is that correct?
A. I don't know his involvement in the Zyprexa project.
Q. If I can direct your attention to the second paragraph. It starts off by saying that these guys were really concerned about the weight gain, not only because of a diabetes risk, but all of the other potential health risks. They initially thought it might simply be a response to improvement in schizophrenia with a few outliers. When they understood that this is seen in nonpsychotic normals and animals on fixed diets, less concern with animals, and that

olanzapine is the worst offender other than clozapine, they advocated a different marketing strategy than we are taking.
Do you see that language, sir?
A. Yes.
Q. Were you informed that Lilly had been advised of that back in 2000?
A. Again, I don't have access to internal documents.
Q. Okay. Did they give you any internal documents showing data from animals on fixed diets?
A. I can't recall if I have -- I've seen hundreds of studies, and I can't recall if those were amongst them.
Q. If an animal is on a fixed diet and gains weight, then it's obviously not gaining weight but of increased caloric intake, correct?
A. I need to know a little bit more about the model, because what happens in animals is often not translatable to humans, particularly as you get further and further away from the human models. So dogs are significantly removed from humans and mice and rats even more so, so it's really difficult to say.

Q. And you don't even know what types of animals were involved in this; you don't know if they're monkeys or dogs or rats or whatever, right?
A. Again, I don't have access to these internal documents and I don't recall that specific study.
Q. If I can direct your attention to about four lines from the only, there's a sentence that starts off, There does not seem much to say. Do you see that, sir?
A. Yes.
Q. Dr. Beasley says: There does not seem much to say about scientific analyses of weight gain. We know it's a weighty problem. When you translate 1 to 2 percent gain of 40-plus kilos into the absolute number based on 5 million patients the number is 50,000 to 100,000. 100,000 people putting on 90 pounds of weight is a lot. You see that language, sir?
A. Yes.
Q. And did Lilly ever provide you the data that forms the background for that statement?
A. I'm not sure what you're asking. This is a statement within an e-mail from this

physician.
Q. Right. Did Lilly provide you any scientific data indicating that at least by 2000, which is, what, eight years ago, there were 100,000 people who had put on 90 pounds of weight after taking Zyprexa?
A. I don't think that's what this statement says.
Q. Well, that's what Dr. Beasley said it says?
A. These are estimates.
Q. And Dr. Beasley -- are you aware of Dr. Beasley's testimony on the subject?
A. In this trial?
Q. Yes.
A. No.
Q. Are you saying that Dr. Beasley was wrong when he did the calculation there, that found that there could be 100,000 people putting on 90 pounds of weight with Zyprexa?
A. This is the first time I've seen such a calculation. I'm not sure what it's based on. It sounds like an informal remark to a colleague. I don't know what this specific number was based on. Was it a scientific sampling? I doubt it.

It's really difficult to comment on someone's e-mail to a colleague.
Q. So you're challenging what Dr. Beasley said and the validity of it even though you don't have data on this one way or another, is that correct?
A. I can't comment on it.
Q. Would you agree -- let's assume for the purposes of agreement that there were, in fact, by 2000, 100,000 people putting on 90 pounds of weight due to Zyprexa. Would you agree that those people would be at increased risk of diabetes?
A. First I would say that 90-pound weight gain is a lot of weight and it's unlikely to be solely responsible because of a drug. There are many patients who gain 90 pounds of weight who are not taking any medications, so these are outliers and I think it's more accurate to determine the average weight gain, not the extreme weight gain, which is unlikely to be related to the medication.
Q. You use the term outliers. That was the thing that the outside endocrinologists thought, too, you see where he talks about that. They

initially thought it might simply be a response to improvement in schizophrenia with a few outliers, a rather naive view, but they ain't shrinks. When they understood that this is seen in nonpsychotic normals and animals on a fixed diets and that olanzapine is the worst offender, other than clozapine, they advocated a different marketing strategy than we are taking.
You see that language, sir?
A. Yes.
Q. By the way, do you know what their marketing strategy was?
A. I'm not familiar with the marketing strategy for this drug.
Q. Okay. Let's get back to the 100,000 people with 90 pounds of weight gain.
If 100,000 people put on 90 pounds of weight that's drug-induced, is that population of folks going to be at increased risk of contracting diabetes?
A. Again, I would take exception to the description of it being drug-induced, because these are outliers.
Q. Sir, I'm entitled to ask you a hypothetical and accept the premise of the

hypothetical, okay? Let's assume that you have 100,000 people who take a drug and that causes 90 pounds of weight gain. Would you agree, sir, that that puts that population of people at an increased risk of developing diabetes?
A. That population would be at an increased risk from before gaining 90 pounds of weight.
Q. And can you give us some sort of ballpark estimate as to what that increased risk would be?
A. Several fold.
Q. Several fold. Well, I believe you testified earlier that you agreed with Dr. Wirshing and with Dr. Brancati who testified that 24 pounds of weight gain would increase the risk 3 to 4 times. If that's the case, then what would 90 pounds be? That would be higher than that, wouldn't it?
A. The relationship is -- may not be linear, so it's difficult to extrapolate from what we know about modest weight gain to more extreme. We just don't know.
Q. You know, you brought up a good point, because that's exactly what Dr. Wirshing and Dr. Brancati said. They said that it's not a

linear relationship. As you gain more and more weight, the rate of increase goes up even more dramatically, doesn't it, sir?
A. I don't think we know that as well as we do some of the more modest weight gain just because the studies for extreme weight gain are not as numerous as other studies.
Q. You don't often see 100,000 people putting on 90 pounds of weight, do you, sir?
A. It's hard to track in research, for sure.
Q. Sir, you would agree with me that putting on 90 pounds of weight is going to increase the risk of diabetes more than three or four times, correct?
A. Several fold. Again --
Q. Several fold times the three to four?
A. Several fold above no weight change. So several fold -- 3, 4, 5. It's difficult to give you an accurate, because these studies have not been adequately done to this degree.
Q. Okay. So you say with 90 pounds of weight gain the risk would be 3 to 4 times higher and with 24 times it would be 3 to 4 times higher. I guess you don't see any difference

between gaining 24 pounds and 90 pounds of weight. Is that what you're telling the jury?
A. I don't think I said that. I said that the data to inform and answer that question is not easily. Again, this is weight gain that occurs over time. So the data we have from these epidemiological study is what happens to an individual over a lifetime of gaining this weight. We really don't know what happens in the short-term because of the issue of beta cell compensation. It could be that the beta cells would compensate more astutely in the setting of more recent weight gain.
Q. Dr. Brancati testified that if you gain -- he was talking in the context of 24 pounds. He said that if you gain 24 pounds in a year, that was going to have a greater impact and more negative impact than gaining 24 pounds over, say, a decade or so. Do you disagree with Dr. Brancati?
A. I disagree because we don't know the answer to that question. You could take arguments from both sides. I don't think we know. And as an endocrinologist who studies this area and sees patients with diabetes, it's

difficult for me to know whether more rapid weight gain is more detrimental or less detrimental than long-term weight gain as regards to diabetes risk.
MR. SUGGS: Your Honor, we're at a convenient stopping place for a break, if now would be convenient for the Court.
THE COURT: Yes, this is a good time. Ladies and gentlemen of the jury, we'll take our second morning break and we'll be in recess for about 15 minutes.
(Jury out.)
(Break.)
(Jury in.)
THE COURT: Please be seated. We are back on the record. All members of the jury are present. Mr. Suggs?
MR. SUGGS: Thank you, Your Honor.
Q. (BY MR. SUGGS) Dr. Inzucchi, in your deposition and I think even today, you testified that it is your opinion that diabetes is probably mainly genetically mediated; is that correct?
A. Correct.
Q. In other words, patients who have a genetic tendency toward diabetes are predisposed

to diabetes, correct?
A. Yes.
Q. Okay. And I believe you also testified that risk factors are additive, correct?
A. With each other?
Q. Yes.
A. Yes.
Q. So if a person has two risk factors, they're much more prone to develop a disease than if they had none or one?
A. Yes, statistically.
Q. And you would agree -- is it a fair statement that weight gain plus genetic vulnerability leads to diabetes?
A. Well, it increases the risk, it doesn't necessarily -- you can't anticipate that a person definitely will or will not get diabetes, but it increases the risk, yes.
Q. If somebody had a genetic vulnerability to diabetes, that would mean that they were predisposed towards getting diabetes, correct?
A. Correct.
Q. Okay. And could you pull up Exhibit 4361, please?
MR. SUGGS: This is 4361; it's not

been previously introduced.
Q. (BY MR. SUGGS) I'm going to hand you what I've had marked as AK4361.
MR. LEHNER: May we just approach for one minute?
THE COURT: You may.
(Bench discussion.)
MR. LEHNER: I want to get the rules straight here. This has not been introduced as an exhibit.
THE COURT: That's the rule. How are you going to get it in through this witness?
MR. SUGGS: Cross-examination, Your Honor.
THE COURT: The question is if it's a nonadmitted document, I don't want it shown up on the board and then have the jury take a look at it and we've got a problem, so --
MR. SUGGS: Okay.
(End of bench discussion.)
MR. SUGGS: Chris, could you take it off the screen for the time being.
Q. (BY MR. SUGGS) Doctor, can I direct your attention to this document which is entitled Issues in Management Planning, Diabetes Final

Draft. Do you see that on the second page there is a listing of core beliefs?
A. Yes.
Q. And the second bullet point there states: Patients taking Zyprexa often experience weight gain which in predisposed individuals can contribute to the development of diabetes.
You see that language, sir?
A. Yes.
Q. And you would agree with that, would you not, sir?
A. Yes, in terms of contributing being the risk factor issue that we discussed this morning, yes.
Q. Well, when you talked about contribute to the development of something, that means that it is playing a causal role, correct?
A. No. You can contribute, but it may not be a cause.
Q. Well, if -- if something contributes, that means that it's a contributing factor, correct?
A. Contributing factor, yes, or risk factor, yes.
Q. Okay. So this document -- you would

agree that patients taking Zyprexa often experience weight gain and in predisposed individuals that can be a contributing factor to their development of diabetes, correct?
A. In an individual patient it's not clear whether the weight gain --
Q. Leave aside the individual patient. Again, we're talking population. Zyprexa was a drug that was sold to millions of people, correct? Correct?
A. I don't know the sales statistics of Zyprexa.
Q. It's been described as a blockbuster drug. It was used by a lot of people, right?
A. If it's a blockbuster drug, I assume it was. I don't prescribe it, so I don't know.
Q. Were you aware that it was the fourth leading drug in the world in terms of sales?
A. I don't know the statistics on sales.
Q. In any event, if we're talking about the population of people that were taking Zyprexa, including the population here in Alaska, patients taking Zyprexa often experience weight gain which in a predisposed individual can be a contributing factor to the development of diabetes, correct?

A. That would be a fair statement.
MR. SUGGS: Your Honor, I move for the admission of 4361.
MR. LEHNER: Your Honor, as we've discussed, it hasn't met the foundation --
THE COURT: I don't think you've laid a foundation.
MR. SUGGS: Okay. I'll go on, Your Honor.
THE COURT: Just because you've read it doesn't make it admissible.
Q. (BY MR. SUGGS) But you do agree with that statement, do you not, as we've discussed?
A. As a hypothetical question, yes. But not as something that's been demonstrated in the clinical trials, as we've discussed.
MR. SUGGS: Chris, can you pull up page 3 of his report, please?
And could you pull up the first bulleted item up there?
Q. (BY MR. SUGGS) And in that second -- third sentence, you say: Most, but not all processes that increase body weight, will, across populations, increase the risk of diabetes.
Do you see that language, sir?

A. Yes.
Q. And, sir, six years ago, in 2002 scientists within Lilly were saying that a fair-minded scholarly evaluation of the evidence would lead to the conclusion that Zyprexa causes weight gain and that Zyprexa-induced weight probably increases the risk of diabetes.
Were you aware of that, sir?
A. I'm not sure what document you're referring to now.
MR. SUGGS: Could you pull up Exhibit 8666?
THE COURT: Is this AK?
MR. SUGGS: AK. Yes, Your Honor. AK86666. It's been previously admitted.
Chris, could you highlight and blow up the last two sentences in the paragraph and then also the two bullet items?
Q. (BY MR. SUGGS) Sir, this is from a June 27, 2002 e-mail from Simeon Israel Taylor to a number of individuals at Eli Lilly and the part that I've had blown up there states: Quote, however, I feel that we need to deal with the scientific facts, whatever they are. Ultimately, I expect that a fair-minded, scholarly evaluation

of the available data is likely to support several conclusions. One, Zyprexa, like other members of the class, causes weight gain; two, like other causes of weight gain, Zyprexa-induced weight gain probably increases the risk of diabetes.
Do you see that language, sir?
A. Yes.
Q. Did the Lilly folks show you this document before you came here to testify?
A. Again, I don't recall seeing any internal documents from Lilly.
Q. And do you disagree with these conclusions of Dr. Simeon Israel Taylor made back in 2002, six years ago?
A. I'm not sure they're conclusions. This sounds like an internal document and I need to know what the context was that this was written in. Was this an interchange between two colleagues at Lilly saying that, hey, this is a drug that causes weight gain? Weight gain is obviously something that's -- you need to be concerned about diabetes. We need to look at this question.
But, again, I'm here to testify to

the view of the scientific literature out there, the studies that we've looked at, and this has not been demonstrated in the clinical trials and mechanistic studies. So this sentence here does not prove that what I said was incorrect. It simply describes a contention of this individual.
Q. Sir, my question was whether you agreed or disagreed with those two statements there. And apparently you disagree, correct?
A. I disagree with statement No. 2 as written.
Q. And, certainly, Lilly has never warned doctors that like other causes of weight gain, Zyprexa-induced weight gain probably increases the risk of diabetes, correct?
A. Are you referring to the package labels or --
Q. Yes.
A. No, that's not something that is in the package label because it's not been demonstrated to be true.
Q. It's not been demonstrated to be true to your satisfaction or the satisfaction of Eli Lilly. In fact, even today Lilly denies that there is any causal relationship between Zyprexa

and diabetes; correct?
A. And the FDA.
Q. Were you aware that the FDA told Lilly that Zyprexa induces hyperglycemia?
A. Again, hyperglycemia is not the same as diabetes.
Q. Sir, my question is: Were you aware that FDA told Lilly that Zyprexa induces hyperglycemia?
A. I'm not aware of what communication you're referring to.
Q. We'll get to that later.
Sir, within days after this e-mail where Dr. Israel Taylor was saying that like other causes of weight gain, Zyprexa-induced weight gain probably increases the risk of diabetes, there was another document generated which concluded that increased blood glucose in the Zyprexa clinical trial was probably causally related. Were you aware of that, sir?
A. Which study are you referring to?
MR. SUGGS: Can you pull up Exhibit 7802, please? Can you blow up the title at the top there, Chris, and then blow up the line for glucose nonfasting high.

Q. (BY MR. SUGGS) Sir, this is data from a study described as Listing of Treatment-Emergent Abnormal Lab Findings in Olanzapine-Treated Patients, Placebo Controlled F1D-MC-HGFU Studies 1 and 2 Combined.
Did you review that study, sir?
A. I reviewed hundreds of studies. I can't recall this specific one.
Q. Don't know if they showed you this one or not?
A. Again, I reviewed hundreds of studies that were submitted to the FDA and this may have been included in that.
Q. But you just don't know one way or the other, correct?
A. As I said, I don't recall specifically this specific page out of a submission to the FDA that may have been several hundred pages.
Q. By the way, it's common, is it not, to conduct laboratory analyses of various things like blood and urine, so on and so forth?
A. Yes.
Q. And it would be customary to do a measurement of high glucose, correct?
A. In most clinical trials, sure, there are

chemistry tests done.
Q. In this study what they found was that 2.2 percent of people exposed to Zyprexa had high nonfasting glucose compared to zero in the placebo group, correct?
A. That's what the line says, yes.
Q. And do you see to the right of that there's letters A --
A. Yes.
MR. SUGGS: Chris, can you blow up the legend down at the bottom so we can show the witness what A means.
Q. (BY MR. SUGGS) Category A means that the event was probably causally related. Do you see that language, sir?
A. Yes.
Q. Did Lilly ever tell you before you came here to testify to this jury that data from this study demonstrated that the event of nonfasting high glucose was probably causally related?
A. I would need to know a little bit more about how the table was formulated.
Q. My question was: Did they tell you this? Did they give you this information before you came to Alaska to testify before this jury?

A. Again, I was given the submissions from Lilly to the FDA, several submissions in which this study may or may not have been included. I don't -- I don't recall specific discussion about this specific line with this specific entry of letter-writing.
Q. Lilly has never told the FDA that any data from any of their studies demonstrates that high blood glucose is probably causally related, have they, sir?
A. I don't understand the question.
Q. Sir, Lilly has never told the FDA that high blood glucose is probably causally related to the administration of Zyprexa, have they?
A. I'm not -- I don't have available to me every discussion between Lilly and the FDA. That's not my purpose here today.
Q. Sir, Lilly has consistently denied that there's any causality between Zyprexa and hyperglycemia or diabetes, isn't that true, sir?
A. As we talked about today, the bulk of the clinical trial data, mechanistic studies, even the epidemiological studies have failed to demonstrate a cause and effect relationship between Zyprexa and diabetes.

Q. Apparently the author of this document thought that this study showed that high blood glucose was probably causally related and no one gave this to you to review, did they, sir?
A. Again, not necessarily. We need to know what causally related meant --
Q. The question was: Did anybody give this to you to review before you came to testify before this jury?
A. I will say, again, that I was given hundreds of pages of submissions from Lilly to the FDA which I reviewed. I cannot specifically recall this specific page, nor can I recall the specific line.
Q. So that would be a no, correct?
A. Depends on what the question you're asking.
Q. My question was whether anybody gave it to you. Your answer is no, you don't recall ever seeing anything from Lilly where they said that hyperglycemia was probably causally related to Zyprexa, correct?
A. The -- the submissions from Lilly to the FDA were given to me by the attorneys. So if this was included in that submission, then it was

given to me.
Q. You don't recall seeing it? They never gave you this, did they?
MR. KANTRA: Objection, Your Honor, we've been over this about four or five times.
MR. SUGGS: I'll move on, Your Honor.
THE COURT: Move on, please.
MR. SUGGS: Your Honor, can I ask him to make a responsive answer to my question?
THE COURT: Yes. Are you saying you just don't know whether you ever got this?
THE WITNESS: I can't recall that.
THE COURT: Do you recall any documents where a causal relationship appears to have been made between Zyprexa and high glucose nonfasting?
THE WITNESS: I can't specifically recall. I looked at these data and came to my own conclusions about causality. But this could be a principal investigator. It could be a director of the clinical trial who has made this judgment. But this would not be my judgment, necessarily.
MR. SUGGS: Thank you, Your Honor.

Q. (BY MR. SUGGS) Dr. Inzucchi, you've testified about the consensus statement.
MR. SUGGS: Chris, could you please pull up Exhibit 2368?
Q. (BY MR. SUGGS) Now, there were a number of people that were invited to speak and present at that panel, correct?
A. Yes.
Q. You weren't one of them, were you?
A. No.
Q. By the way, this was a consensus statement not just of the American Diabetes Association, but also of the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, correct?
A. Yes.
Q. And you talked earlier today in response to Mr. -- questions from Mr. Kantra that you had been on an ADA consensus panel of one sort or another?
A. Yes.
Q. Have you ever been on a consensus panel where you had four different medical associations convening the panel?

A. Yes.
Q. And the speakers, the panel of experts at this I believe you testified in your deposition that Mr. Fibich took, that you knew about half of them, right?
A. I don't recall saying that.
MR. SUGGS: Chris, can you go to -- can you go to the last page, please, and can you blow up the paragraph there at the top on the left about the consensus panel.
Q. (BY MR. SUGGS) I believe you testified that you know a number of those individuals, in fact, the ones who were the endocrinologists, is that correct?
A. Your question was whether I knew the presenters. These were the authors --
Q. I'm sorry.
A. Okay.
Q. In any event, these were the experts who were on the panel who were hearing the evidence and hearing the presentations, correct?
A. Correct.
Q. And you knew all of them or some of them?
A. Some of them.

Q. Okay. About half?
A. Three, possibly four.
Q. And you testified in your deposition that you respect their abilities as endocrinologists, correct?
A. The ones that I know, yes, of course.
Q. The ones -- was this a panel just of endocrinologists, or did it also include psychiatrists?
A. I'm not exactly sure, but I would assume that because the convening bodies represented both psychiatry and endocrinology, there were psychiatrists on this panel.
Q. This panel of experts reviewed all of the known literature in the English language and then heard presentations from 14 experts, the FDA and representatives of the drug companies that manufactured atypical antipsychotics, correct?
A. Yes.
Q. By the way, were you aware that Dr. Allison, Dr. David Allison was one of the presenters?
A. Yes.
Q. And he did one of the studies that you said that you relied on most heavily, correct?

A. Correct.
Q. And he would have presented the data for that, correct?
A. I believe so, yes.
Q. Also Patrizia Cavazzoni was another presenter there, correct?
A. Yes.
Q. And she would have presented her data as well, correct?
A. I would assume so, yes.
Q. And can you look at --
MR. SUGGS: Can you turn to table 2, please, Chris?
Q. (BY MR. SUGGS) And you've testified to the jury this morning that despite the fact that the ADA consensus statement came out with these conclusions which are summarized in that table, you disagree with them, correct?
A. Some of these conclusions, yes.
Q. Okay. You disagree that olanzapine has a higher risk of weight gain than another, for example, risperidone, quetiapine, aripiprazole or ziprasidone?
A. No, my disagreement concerned the second column.

Q. So you disagree that there is a risk for diabetes with olanzapine, correct?
A. I believe the risk for diabetes is in patients who take olanzapine because they have psychiatric illness and schizophrenia, so it depends on how you phrase the question. The issue is whether olanzapine adds to that risk and that's, I think, still very controversial and I'm not sure we know the answer to that question.
Q. Apparently it wasn't controversial for the ADA consensus panel, correct?
A. It was definitely controversial. That's why consensus panels are convened.
Q. When they got done, what they did was they published this article which appeared in February, 2004, and in this table they said there was an increased effect for the risk of diabetes with olanzapine, correct?
A. That's what they felt.
MR. SUGGS: Can you turn to the summary section, please? It's the last page -- I take it back the -- page 5 -- the page just before that in the right-hand column. Second paragraph is all I need blown up.
Q. (BY MR. SUGGS) And this panel of

experts, after hearing all of -- by the way, this panel not only heard presentations, they reviewed all of the known literature that was published in English at that time, correct?
A. I don't know what they reviewed. They certainly attended the conference.
Q. Well, according to the article on the first page -- you don't have to go there, Chris -- it says in addition, before the conference, the consensus panel was given copies of most of the known peer-reviewed English-language clinical studies published in this area as well as additional articles present, animal studies, other papers and abstracts were reviewed at the conference.
Do you have any basis to dispute that?
A. No.
Q. And then in the summary section they say that: Clozapine and olanzapine are associated with the greatest weight gain and the highest occurrence of diabetes and dyslipidemia.
Correct?
A. Yes. Associated with.
Q. And they aren't talking about just a

risk of diabetes; they're talking about the highest occurrence of diabetes, correct?
A. They're talking about a risk of diabetes being an association, not a cause. There's nothing about cause here.
Q. The cause is implied in the whole paragraph. They go on to say, Risperidone and quetiapine appear to have intermediate effects.
Effects are -- result from causes, correct?
A. That's how I use the word. I think this --
Q. You think they were using the English language differently than you were, sir?
A. No, but I do think at the time that this was written there was a lot of controversy and this was their best effort to come to some consensus as to what we need to be looking for. But the majority of this document actually focused on what we need, what data do we need to actually prove or to demonstrate actually what's going on.
Q. Sir, were you aware that after this conference the ADA, American Diabetes Association, issued a press release regarding the

consensus panel?
A. That follows most consensus panels, yes.
Q. I'm going to hand you what I'll marked as the next exhibit. I'm not quite sure what the number is. I've got to look at what you've got up there.
THE COURT: 10176?
MR. SUGGS: I think it's AK10177. Is that right, Mark?
THE CLERK: 10177.
Q. (BY MR. SUGGS) And did you see this press release when it was issued, sir?
A. No.
Q. You were on the board of the American Diabetes Association at that time, were you not? Or did that come later?
A. I'm not on the board of the Diabetes Association. I'm on the professional practice committee.
Q. Okay. So you're a member of a committee of the association but you're not on the board, or did I misspeak?
A. It's semantics. The professional practice committee is one of the committees in the American Diabetes Association. There is an

over board that controls all the actions of the ADA. I don't see sit on that.
Q. And the title of this -- I'm going to put this up on the ELMO.
THE COURT: Again, are we getting this?
MR. SUGGS: Pardon?
THE COURT: Before we put it up on the ELMO is it being admitted?
MR. SUGGS: I offer Exhibit AK10177 -- AK10177.
MR. LEHNER: No objection, Your Honor.
THE COURT: AK10177 is admitted.
Q. (BY MR. SUGGS) And, Doctor, the title of this press release is Antipsychotics Raise Obesity, Diabetes, and Heart Disease Risks. Correct?
A. Yes, that's what it says.
Q. And if some factor raises a risk, that means that it has an increasing effect, correct?
A. It raises -- it raises the risk. Across the population, more people will develop that disease, yes.
Q. And what does the phrase "lead to" mean?

A. I need context.
Q. Well, when you were talking before, you said that we couldn't show causation unless we could show that a drug led to damage to the beta cells, correct? You know what the phrase led to meant in that context, right?
A. That would be supportive evidence of causation if you could actually demonstrate mechanistically what's going on at the level of the pancreas, yes.
Q. If I could direct your attention to the first paragraph, it states: People who take antipsychotic drugs for the treatment of a variety of mental illnesses may be at increased risk for obesity, diabetes and high cholesterol, all of which can lead to heart disease. Because of this, a joint panel of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity has issued a consensus statement asking doctors to carefully screen and monitor patients on these medications for signs of rapid weight gain or other problems that could lead to diabetes, obesity and heart disease and refer

them to specialists, if necessary.
Correct?
A. That's what it says, yes.
Q. What they're talking about there is the problem of rapid weight gain leading to diabetes, correct?
A. Yes.
Q. Okay. And clearly, they are thinking in a causal way, are they not?
A. I'm not sure what they're thinking. The language is association.
Q. They talk about something leading to diabetes, correct?
A. Weight gain, yes, weight gain. We know that weight gain is a risk factor for diabetes.
Q. And we know that Zyprexa causes weight gain, correct?
A. (Witness nods head.) But what has not been demonstrated is Zyprexa causing diabetes.
Q. We know that Zyprexa can cause massive amounts of weight gain in some individuals, in some instances more than 80 pounds, correct?
A. I'm not sure we know that specifically. Patients in those clinical trials, some gained weight, some lost weight. Patients not in

clinical trials can gain 80 pounds as well.
Q. We saw in the e-mail from Dr. Beasley that he felt back in 2002 it could be said definitively that Zyprexa causes weight gain. Do you remember that?
A. We've spoken before about Zyprexa causing weight gain. That's not something that I'm going to disagree with.
Q. If I can direct your attention to the third paragraph, this press release states: The panel concluded that, quote, there is considerable evidence, end quote, that treatment with SGAs can lead to rapid weight gain and that most of the weight gained is fat.
Correct?
A. Yes.
Q. And as we saw from your quote from the letter to the editor, you wrote back in 2003, with that begins diabetes --
A. That was in reference to lipid levels in blood.
Q. Was that quote from 75 years ago talking about lipid levels in the blood or talking about obesity?
A. It was referring to both, but we used

that in the context of the article which is about lipid levels and cardiovascular diseases.
Q. This press release goes on to state, studies also show that association between SGAs -- SGA stands for second-generation antipsychotic, correct?
A. Yes.
Q. -- studies also show an association between SGA use and the development of prediabetes, diabetes and elevated blood lipid levels.
And you've testified in your deposition that you didn't even believe there was an evidence of an association between Zyprexa and diabetes, correct?
A. No, I did not say that.
Q. Do you believe there is an association?
A. I said that there are some studies that have associated Zyprexa with the develop of diabetes, some of the observational or epidemiological study that we reviewed today.
Q. You said some studies have shown that. Where do you come down -- is there an association between Zyprexa and diabetes?
A. Overall, the observational data point in

many different directions, so there are data out there that have associated Zyprexa with diabetes, but taken in the contrast of the clinical trials and the mechanistic studies, there's no convincing data that there's a causal association.
Q. In your view there is not even an association between Zyprexa and diabetes?
A. There is an association between Zyprexa and diabetes insofar as patients who take Zyprexa have schizophrenia and schizophrenia is associated with diabetes.
Q. In some cases SGA use have been associated with diabetic ketoacidosis, DKA, which can be life-threatening.
Did I read that correctly?
A. Yes.
Q. Is that the same ketoacidosis that we talked about earlier?
A. The one that's associated with type 1 diabetes.
Q. And the ADA points out here that it can also occur in the context of atypical antipsychotics, correct?
A. That's what they point out, yes.

Q. They also go on to state, the paragraph below that: The panel also concluded that the SGAs differ in their risk profiles and that some SGAs such as clozapine and olanzapine, while effective treatment options, raise a greater risk of weight gain, diabetes and lipid disorders than others.

Correct?

A. That's what it says, yes.

Q. And then they go on to say below that -- they state that the risks that are reviewed here in this study should influence choice of medications, correct?

A. Yes.

Q. Okay.

MR. SUGGS: Scott, that's all I'm going to do with that.

MR. LEHNER: Your Honor, can we approach for one minute?

THE COURT: You may.

(Bench discussion.)

MR. LEHNER: We have informed Plaintiffs that there is a time for -- this witness has a time constraint, and I think we've been repeating things over and over again. I'm

concerned about the -- about the motive, actually.

MR. SUGGS: To the extent I've repeated things it's been because he hasn't been responsive to the questions.

MR. LEHNER: He has a flight at 4:30 this afternoon.

MR. SUGGS: I'm coming down to the last --

THE COURT: Let's get done with our discussion and finish this up.

(End of bench discussion.)

MR. SUGGS: Your Honor, can I publish AK10177 to the jury?

THE COURT: You may.

Q. (BY MR. SUGGS) Doctor, I'm mindful of the fact that you need to catch a plane, and since I haven't been home in a month, I'm sympathetic for anyone who wants to get home. So I'll try to move it along here.

A. Thanks.

MR. SUGGS: Chris, could you pull up Exhibit 10094? This is the March 27, 2002 letter on -- pardon me -- March 27, 2007 letter that the jury has heard considerable testimony

about.

Q. (BY MR. SUGGS) And I believe you saw this at your deposition, did you not, sir?

A. Yes, this I recall seeing.

Q. You saw in this that the FDA informed Lilly in March that they were concerned that the labeling for Zyprexa is deficient with regard to information about weight gain, hyperglycemia and hyperlipidemia that is associated with olanzapine use whether taken alone or in combination with fluoxetine, correct?

A. Yes.

Q. I wanted to ask you some specific questions with respect to the first full paragraph on page 2.

MR. SUGGS: If you can blow that up, Chris.

Q. (BY MR. SUGGS) In this letter there is discussion of some data that Lilly had submitted to FDA. Do you recall reviewing that?

A. The data, yes.

Q. And what they did -- what the FDA describes in this paragraph is comparisons between placebo and people who were exposed to OFC or the combination of olanzapine and

fluoxetine, correct?

A. Yes, right.

Q. And by the way, it's clear that the FDA's concerns about hyperlipidemia and diabetes and stuff that were expressed in this letter pertain to the Zyprexa portion of the drug, not the Prozac, correct?

A. That's what my impression is, yes.

Q. Okay.

And in this paragraph they talk about two comparisons. One is a comparison between the incidence of hyperglycemia in excess of 200 milligrams per deciliter in patients who were exposed to the Zyprexa combination drug and placebo, correct?

A. Yes.

Q. And that 200 milligrams --

MR. SUGGS: Can you blow up, Chris, so the jury is sure exactly what we're talking about here -- actually, can you start the third line down, the sentence that starts "for example".

Q. (BY MR. SUGGS) For example, we note that your proposed Symbyax label includes information only on proportions of patients who

are relatively normal at baseline with regard to random blood glucose, less than 140 milligrams per deciliter, i.e., 2.9 percent of such patients receiving OFC had on-treatment levels greater than or equal to 200 milligrams per deciliter compared to .3 percent of placebo-treated patients.

Stop right there, Chris.

Now, what that's saying is that there was essentially a tenfold increased incidence in hyperglycemia above 200 milligrams per deciliter for the patients who were exposed to the Zyprexa drug versus those who just got placebo, correct?

A. That's what it says, yes.

Q. And that tenfold difference is about the same -- that's a relative risk of 10, correct?

A. I wouldn't use that term in analyzing adverse event data from clinical trial, no.

Q. Well, this clinical -- you've talked before about how a clinical trial is the gold standard for scientific evidence, correct?

A. But your use of the term relative risk is not --

Q. Okay, that's usually used in an

epidemiological list -- but let's talk about this study. This study is supposedly, according to your lights, a gold standard study. This is from a random prospective controlled clinical study, correct?

A. Yes.

Q. And what this gold standard test found in humans was that the patients who were exposed to Zyprexa who had previously had relatively normal blood levels had a tenfold higher incidence of hyperglycemia as compared to placebo, correct?

A. That's -- again, that's what the sentence says. I've looed at these data, and the data are a bit misleading as they are presented here, because there are some patients who are in these categories that actually get better with Zyprexa. Some certainly get worse. So this is a snippet from that clinical trial. There's nothing about numbers of patients here. 2.9 percent could be 1 out of 18 patients.

We need to sit down together and review the actual clinical trial data that led to this sentence. So, in -- as it's read, it's accurate. But it's difficult to interpret

without seeing the numbers in front of me.

Q. The answer to my question is yes, correct?

A. I forgot the question.

Q. I thought you might. What this shows is that the folks who got Zyprexa had a tenfold higher incidence of hyperglycemia than the folks who took placebo, correct? Yes or no?

A. That's accurate, yes.

Q. And that level of hyperglycemia that they had wasn't just some mildly elevated level? It was 200 milligrams per deciliter, correct?

A. The problem here is these are nonfasting -- these are nonfasting data.

Q. I realize that, sir. My question is: The level that they had there was 200 milligrams per deciliter nonfasting blood glucose, correct?

A. Correct.

Q. And that is a level that is diagnostic for diabetes according to the American Diabetes Association, correct?

A. Incorrect.

Q. Well, if you were going to use random blood glucose --

A. Yes.

Q. -- to determine whether somebody has diabetes, the cutoff level above which is diabetes, if you're using random blood glucose is 200 milligrams per deciliter; is that correct?

A. You're making many errors here. You cannot use these numbers to diagnose diabetes in the context of this clinical trial. The diagnosis of diabetes is made upon two repeated values greater than 200 in conjunction with symptoms.

Q. I understand that, sir. But my question is the level of the cutoff that you use for random blood glucose by the American Diabetes Association to determine whether or not someone has diabetes is 200 milligrams per deciliter using the random test, correct --

A. Yes.

Q. -- as compared to 126 which is the fasting --

A. That's what the cut point is.

Q. That's all I'm after. You had here a tenfold increased incidence of the folks who had Zyprexa who were above that cut point as compared to placebo, correct?

A. In the context of this clinical trial,

yes.
Q. And this clinical trial and that analysis was actually done by Lilly, was it not?
A. Yes.
Q. Okay. It wasn't done by FDA? This was an analysis that was done by Lilly on that data, correct?
A. Correct.
Q. And was it your understanding also that this data that came from -- pardon me -- the data that formed the basis of that had been in Lilly's possession or they started collecting that data as early as 2002?
A. Again, I don't have access to internal Lilly documents. I don't know what the date of this study was.
Q. And then they have another comparison. This one we've just been talking about is the comparison between Zyprexa and placebo for folks who had relatively normal blood levels, correct?
A. Less than 140 if it was fasting would not be normal. Less than 126 would not be normal.
Q. At least as described in the FDA those were the relatively normal at baseline folks,

correct?
A. Again, it's critically important that you distinguish between fasting and random glucose levels because the cut points are very different.
Q. This whole paragraph is talking about nothing but random -- they're using random blood glucose levels in tests in all of this, correct?
A. I believe so, yes.
Q. Okay. So, we've talked about the one comparison where they were looking at folks who had relatively normal blood levels at baseline according to FDA, but they do another comparison here between the folks who use Zyprexa and the placebo for folks who had somewhat elevated blood levels, correct?
A. Yes.
Q. They note here that 46 percent of patients who were borderline to high had such on treatment levels compared to only 5 percent of placebo-treated patients, so again, it was about a tenfold higher increase to the folks exposed to Zyprexa, correct?
A. Yes.
Q. Almost 46 percent -- not almost. It

says 46 percent of the people who were borderline to high went up above that 200 milligram deciliter cut point, right?
A. It's extremely misleading to present percent data without looking at the specific numbers. 46 percent --
Q. Sir, can you answer my question?
A. I'm trying to, but it's important to understand that 46 percent, if it's two out of four patients, that's 50 percent. You really need to know what the baseline risk is, and also what happens to the people in the other categories.
MR. SUGGS: Judge, can I get an instruction for him to answer my question.
THE COURT: You need to listen to the question he's asking as that one. These guys want you to explain things, they'll do that. We'll get you on the plane today instead of tomorrow if you listen to his questions and answer the questions he's asking.
Q. (BY MR. SUGGS) In the folks who had borderline to high levels of blood glucose at the start of the experiment, 46 percent of them went up above that 200 per -- 200 milligram cut point,

right?
A. Yes.
Q. As compared to only 5 percent of placebo, right?
A. Yes.
Q. Tenfold increased incidence, correct?
A. Yes.
Q. By the way, in studies of cigarette smoking, do you know how much the risk of cancer is increased in folks who smoke cigarettes as opposed to nonsmokers?
MR. LEHNER: What's the relevance?
MR. SUGGS: It's about nine or ten times higher.
THE COURT: What's the relevance?
MR. SUGGS: It's a comparison, Your Honor, between this type of finding and the evidence regarding cigarette smoke.
THE COURT: I'll sustain the objection.
Q. (BY MR. SUGGS) Now, Doctor, you testified that you were not aware that the FDA after -- getting this data wrote to Lilly and said that it was their view that Zyprexa induces hyperglycemia. Do you recall saying you weren't

aware of that?
A. That specific letter or communication, no, I'm not aware of it.
MR. SUGGS: Chris, can you pull up 10108, please?
Q. (BY MR. SUGGS) Doctor, you are aware that FDA made Lilly change their label in 2007, correct?
A. Yes.
Q. You were aware that the FDA told Lilly that they wanted to change the label in order to protect the public health?
A. I have not heard those words, no.
Q. If I could direct your attention to the third paragraph in Exhibit 10108, the last two lines state, in part -- well, let's start at the top of the paragraph. It said, we have reviewed the data you have submitted thus far as well as the available literature and we would like to request that you make labeling changes listed below pertaining to the effect of olanzapine and Symbyax on body weight, lipids and glucose.
Do you see that language, sir?
A. Yes.
Q. Were you aware that in the intervening

months between March of 2007 and August 28th, the date of this letter, Lilly repeatedly told FDA they did not believe that any labeling changes were necessary?
A. Yes.
Q. Who was it that made you aware of that? Was that the lawyers --
A. I'm sorry. I lost the train of thought there. Say that again. The request --
Q. Were you aware that between March of 2007, the date of the prior letter, and August, 2007, the date of this letter, that Lilly told FDA repeatedly that label change was not necessary?
A. I'm sorry. Again, I'm not aware of those internal communications at that level.
Q. If I can direct your attention to the last line -- last two lines in this letter, it states: We believe that it is in the best interest of the public health to make interim labeling changes now based on the data that we already have available.
Do you see that language, sir?
A. I'm sorry, I lost your paragraph.
THE COURT: The last sentence.

Q. (BY MR. SUGGS) Looking at the last two lines, where it says: We believe that it is in the best interest of the public health to make interim labeling changes now based on the data that we already have available.
And you were unaware that that was the case; is that correct?
A. I don't recall seeing this specific letter previously.
Q. If I could direct your attention to the following page --
MR. SUGGS: Chris, can you blow up that first paragraph under the heading Hyperglycemia, and highlight the last sentence?
Q. (BY MR. SUGGS) By the way, Doctor, you testified several times before that the word induced means caused, correct?
A. Yes, I think --
Q. In this letter, FDA stated: Olanzapine and clozapine treatments have been associated with a greater potential to induce hyperglycemia than other atypical antipsychotics.
Do you see that language, sir?
A. Yes.
Q. And you disagree with that, don't you,

sir?
A. Well, no -- the --
Q. You do agree with it?
A. It depends if you're pertaining to the clinical trials where these were compared and some of the studies were mentioned in Cavazzoni and in Allison, olanzapine, for instance, was associated with a higher glucose level so the glucose did increase. But if you're using hyperglycemia as a threshold phenomenon based on the published literature, this would be inaccurate.
Q. Well, sir, that literature on -- pardon me -- the scientific findings that we discussed before that were in the March, 2007 letter showing a tenfold increased incidence we've talked about?
A. Yes.
Q. That's never been published by Lilly, has it, sir?
A. I don't -- I don't believe those new data have been published yet, no.
MR. SUGGS: May I have a moment, Your Honor?
THE COURT: You may.

(Discussion off the record.)
MR. SUGGS: Your Honor, State of Alaska passes the witness.
THE COURT: Mr. Kantra.
Mr. Kantra, can you give me a sense of how much time you've got?
MR. KANTRA: I would estimate I have no more than 10 to 15 minutes.
THE COURT: Anybody got any critical things -- what time?
VENIREPERSON: I have a 2:10 appointment, Your Honor. I can be five to ten minutes late.

REDIRECT EXAMINATION

Q. (BY MR. KANTRA) Dr. Inzucchi, I want to show you, first, what the State showed you earlier which was marked as AK10175 which was the Hausknecht study. And this was just to refresh your recollection on this. This was the study on rats that was discussed with you. And if you -- if look at the end of that article, and you read along with that last sentence that states that: Properly designed clamp studies in human subjects could confirm whether the acute effects we observed preclinically translate to schizophrenic

patients.
A. Yeah.
Q. And that's consistent with your understanding of why relying upon animal studies to make judgments about causation is not appropriate.
A. Yeah, you'd always defer to the human studies.
Q. You also told us in regard to another study, which was the Sacher study, and that was again, just to remind you, the euglycemic clamp study, right?
A. Yes.
Q. This was AK10176. And you told the jury and the Court that you believe that study was invalid, that the conclusions that were reached in that study were invalid?
A. Correct.
Q. And I want to show you in particular page 5 of the document. And I want to show you -- zooming in and zooming out -- I just want to get both.
Can you tell the jury why it is your belief that this study is not valid?
A. Well, for a very simple reason. On the

top panel there are two lines superimposed and these are in patients who are getting ziprasidone. This is the comparative drug. You can't really distinguish the two lines because they're so identical that they're superimposed.
So one line represents baseline, so that's before exposure to the drug, and the other indicates ten days after ziprasidone. This clearly shows that ziprasidone has no effect on insulin sensitivity. Remember this is the euglycemic clamp that is testing insulin resistance, versus insulin sensitivity. So that's what you'd like to see if you don't think that a drug is causing any perturbations in that measure.
The bottom panel shows what happens with -- or what the authors state happens with olanzapine. There's something very, very curious in this graph. The first is that the baseline which is the top line that is heading upwards, that is a very curious result from a euglycemic clamp. The euglycemic clamp, you should be in steady state at about 40 minutes.
Q. What does steady state mean?
A. That means that your glucose uptake --

this is how much glucose -- remember, we're giving glucose to prevent people from getting hypoglycemic. And this indicates how much glucose is being uptaken by peripheral tissue such as muscle, so that glucose uptake should be smooth as can be. After 20, 40 minutes it should be very, very smooth.
Q. And instead, what do you see here?
A. Well, it's climbing.
Q. What does that tell you?
A. I don't know what it's telling me. It's just saying that at 100 minutes the glucose uptake in the baseline test was much higher than at the beginning of the test. So this is not a steady state. I can't tell you what happened in this study, whether the procedures weren't followed.
It's very difficult to explain why the glucose uptake would be heading skyward in this steady state study. Then you get to the open circle line which is after ten days of olanzapine therapy. And they're showing that the glucose uptake is at a certain range. It's not possible to compare these two lines.
This is the conclusion of their

study and they actually point out that this is a negative to their study in the discussion, but you can't compare these two lines. You need to compare two steady state lines. You can't compare one line that is not in a steady state to the other line.

If you forget about the line that is going upward, and you just compare the glucose uptake in the olanzapine arm, it's very similar to what you'll see in the ziprasidone arm. So it's about -- glucose uptake of about 5. So this tells me that you can certainly interpret the ziprasidone part of the study. Ziprasidone clearly does not lead to insulin resistance. You can't interpret that line. I believe that is one of the reasons this was not published in a metabolic journal. This would not have passed peer review in a metabolic journal.

MR. SUGGS: Objection, Your Honor. Speculation.

THE COURT: I'll let the testimony stand.

Q. (BY MR. KANTRA) You were also asked, Dr. Inzucchi, about weight gain and the extent to which diabetes either develops or doesn't develop

as a result of weight gain. Just to be clear, you're not aware of evidence that establishes that the weight gain associated with Zyprexa leads to diabetes, right?

A. No, as we've reviewed this morning.

Q. Now, you were also asked or I believe you were asked on cross-examination about whether or not there were clamp studies that contradicted Lilly's results. We've talked about the Sacher study, which as you said was a euglycemic result. I want to talk about the hyperglycemic clamp which was the other clamp study we talked about, and if you remember, that was the one that talked about effects on the pancreas, right?

A. Yes. To see how well the insulin can be stimulated by hyperglycemia.

Q. And that would be the fundamental test to figure out whether a drug actually had a direct effect on the pancreas' ability to produce insulin?

A. Yes.

Q. Which is your view about the fundamental reason why diabetes occurs, correct?

A. Yes. That's why diabetes occurs, yes.

Q. And nothing that has been shown to you

today contradicts the hyperglycemic clamp study that we reviewed earlier, correct?

A. No, it has not been refuted.

Q. Now, you were also asked a question about the extent to which weight gain of a magnitude of 80 or 90 pounds, what that might lead to in terms of an increased risk of diabetes. Do you remember those questions?

A. Yes.

Q. You responded by saying that you thought the increase in risk might have been about a three to fivefold increase?

A. I think I said several fold. I don't know specifically what that would lead to. It's several fold above the normal anticipated risk of diabetes.

Q. Okay. And would that kind of increased risk of diabetes, if a drug was actually causing diabetes, would you expect to see that in the clinical trials that have been conducted to date?

A. If it was leading to 90 pounds of weight gain, within a few hundred patients, you would see epidemics of diabetes, and that's not what you see.

Q. Okay. Doctor, why would a physician

keep a patient on a drug if they'd gained up to 90 pounds?

MR. SUGGS: Objection; speculation.

THE COURT: I think this is pushing the line. He doesn't --

MR. KANTRA: In regards to his consultations that he's done, if he knows.

MR. SUGGS: What drug? What patient?

THE COURT: Let's tie it to Zyprexa, which he doesn't prescribe. I'm going to sustain the objection.

MR. KANTRA: I'll move on.

Q. (BY MR. KANTRA) Doctor, you also were asked about a Japanese label and you were presented with information that there had been a contraindication for patients with diabetes?

A. Yes.

Q. Is it your intention to go back and in your work with various psychiatric institutions advise physicians that they should be not prescribing Zyprexa to their patients?

A. No. Particularly if it's working well in patients, no.

Q. You were also asked a couple of

questions about the extent to which -- I'm sorry. I'm going to start over again.

You were shown a letter in regards to Symbyax data, right?

A. Yes.

Q. Okay. And Symbyax is a combination product between olanzapine or Zyprexa and fluoxetine or Prozac, right?

A. Yes.

Q. And that data that Mr. Suggs showed to you as you stated, showed a tenfold difference in the rates of elevations in glucose levels, correct?

A. Correct.

Q. Now, you've also reviewed other data. You've reviewed fasting date from placebo-controlled trials regarding Zyprexa, haven't you?

A. Yes.

Q. And that data doesn't show a tenfold difference, does it?

A. Correct.

Q. Okay. You were also asked a question about an August 28th letter that was sent to Lilly by FDA, right?

A. Yes.

Q. And Mr. Suggs asked you about a line that letter in which there was a statement about olanzapine and clozapine having the potential to produce hyperglycemia at a greater rate than seen on other agents, correct?

A. Yes.

Q. Okay. And have you reviewed the 2007 label that actually was issued with the FDA's approval in October of 2007?

A. Yes, I have.

Q. And does that letter -- does that labeling, current labeling for this drug say that olanzapine induces hyperglycemia?

A. I would have to refresh my memory on that. I believe the wording is that it has been associated with increases in blood glucose, levels or glucose elevations.

Q. Associated with glucose elevations not inducing hyperglycemia?

A. Not inducing hyperglycemia, so it's not just semantics. Again, increasing the blood glucose can occur in the normal range. Hyperglycemia is a threshold; diabetes is another threshold.

Q. Okay. And lastly, let me ask you, there have been many questions today about increasing the risk for diabetes versus causing diabetes. Is there a difference, in your mind, between an increase in the risk of diabetes that's associated with a particular medication, and a medication actually causing diabetes?

A. Yeah, absolutely.

Q. What is that difference?

A. Well, diabetes is a disease of the pancreas. Things can make it more likely to occur. If you're overweight, you're more likely to get diabetes, but the overweight -- the obesity, the increased pounds is not the cause of the diabetes. The diabetes occurs when there's an underlying predisposition or genetic likelihood for beta cell decompensation. Pancreatic decompensation in the face of that -- those increased pounds and presumably insulin resistance. It's a risk factor. It's not the cause of diabetes.

Q. Thank you, sir.

MR. SUGGS: Your Honor, I could have lots of questions but in the interest of time, we'll pass.

THE COURT: Ladies and gentlemen, again, this would be the time to have you ask questions if you need to. I want to ask you about the interest of time. If at least one of you members have questions, if anyone have questions they really, really want to ask, that's fine with me. I hate to have to do anything that suggests you shouldn't ask questions, but I do remind you about the time.

So if anyone has questions, we'll try to get them asked of the doctor at this time.

No? Okay. Thank you. Ladies and gentlemen of the jury, then, that brings us to the end of our trial day today. Am I correct that tomorrow we'll resume with the State's deposition? No out-of-order witnesses?

MR. ALLEN: Yes, we'll finish up tomorrow.

THE COURT: We should finish up the State's case tomorrow. Once again, before you leave, I'll remind you, please do not discuss the case with anyone or have anyone discuss it with you. Please keep an open mind until you hear all the evidence in the case. Please do not read any newspaper articles or listen to TV or radio about

this case or do any Internet research.
I'll see everyone tomorrow at 8:30. Have a nice afternoon.
(Jury out.)
THE COURT: We are outside the presence of the jury.
MR. KANTRA: Your Honor, can Dr. Inzucchi step down?
THE COURT: The doctor may step down. Have a nice flight back, Doctor. Please be seated, too.
Anything we need to take up before we recess?
MR. SUGGS: One quick question, Your Honor. I think the only exhibit that I moved into evidence was one that I've already, in fact, published. Those I marked for identification, but I'm assuming Mr. Borncamp [sic] will want to hold onto those if I put a sticker on them.
THE COURT: Mr. Borneman --
MR. SUGGS: Mark. I'm sorry.
THE COURT: Yeah. There were a number of articles that were marked for discussion with the doctor and clearly were

discussed. In the past we've been having articles come in more for notice. These articles weren't just discussed for notice. They were discussed for the truth of the matter.
MR. SUGGS: Your Honor, the timing of them was such I would find it difficult to argue for notice because they were primarily 2007 articles.
THE COURT: They certainly should be retained for identification purposes, but if there's anything else you want to get in, you need to let me know specifically.
MR. SUGGS: Can I get the pile there, Your Honor, and just double-check that?
THE COURT: Sure, you can look it over and we'll take it up first thing in the morning. I think only one -- I do agree that there was only one new exhibit, which I believe was the press release following the --
MR. SUGGS: AK10177, we've already had that admitted and published, Your Honor.
THE COURT: I think that's the one that I recall that hadn't been previously admitted that was admitted as a new exhibit.
Anything else, then, that we need

to take up?
MR. ALLEN: Did you get your -- State memorandum regarding UTPA penalty --
THE COURT: I just did.
MR. LEHNER: Your Honor, just for planning purposes, I know we have approximately an hour and 15 minutes of video tomorrow. You were talking about wanting to introduce some exhibits. Is it your intention that we would have -- do whatever applications we want to do and call a witness at the end of that period. I just want to know what we should have available tomorrow.
THE COURT: I'm assuming if we have an hour and 50 minutes and by the time --
MR. LEHNER: And we may play a couple of videos in ours so we may have a total of like two hours. We may play a couple of video clips.
THE COURT: I would assume that by shortly after our morning break, sometime around 10:30 or 11:00, allowing some time for applications and stuff, that Lilly should prepare to start putting on its case.
MR. ALLEN: I have exhibits I need

to get in.
THE COURT: Even with that, if you've got an hour and 45 and 50 minutes and it takes some time for the applications, assuming that we get started close to 8:30, by the time that gets done and the exhibits get done and stuff, I'm figuring two and a half hours for all of that, and some of these things we can deal with while the jury is out on its break. We'll just have a longer morning break --
MR. FIBICH: Your Honor, there's one other issue dealing with the statutory penalties, I think we need to have some insight from what the Court thinks in the morning. That may change what we need to do, and if the Court feels that the penalties are to be assessed by the jury, then we would want to rest subject to calling the State's witness --
THE COURT: Let me read your brief and stuff. I'll tell you preliminarily. First, there is a question -- Lilly is raising a question as to whether or not the statutes, the penalties apply. So that's got to be decided. To the extent it applies, I certainly want the jury to be able to in some way describe through

interrogatories on -- first the jury has to decide whether there is a violation of the UTPA. If there is, we probably would want the jury to decide in some ways that would let us identify what the violations are, at least, if we need to down the road, and then we can discuss whether we need to what have some testimony about how many. But if, for example, the jury were to be asked interrogatories as to whether or not each of the product labels is a -- I want to have some way to know what the violation actually is that they're finding if they find a violation so that there's a way to calculate numbers.

MR. FIBICH: Your Honor, I think the point is this, and I agree with you. The question becomes we're going to rest subject to calling Mr. Campana if we feel the need to put on testimony as to number -- as to number of violations. So, if the Court is not inclined to allow us that latitude, then we're going to need to call Mr. Campana before we rest tomorrow.

THE COURT: What I'm sort of hearing is we may get started a little late tomorrow, because we may have some -- let me read both of your submissions and then we probably

ought to have some discussion.

MR. LEHNER: Truly, that sounds like that's going to be necessary. I'm just concerned about whether or not we are going to have one more witness to the State's question, depending on the discussion or depending on the decision, it seems a little amorphous at the moment. If the State is going to rest, I think the State is going to rest, subject to, I haven't heard that procedure.

MR. ALLEN: We will rest subject to if a determination has to be made, we have the orderly presentation of witnesses. They called them out of order. That's common. If we need to determine that, we need to determine that.

THE COURT: They're going to make applications following your resting that I assume, and so everybody -- I need to give both of you an opportunity to argue how you could propose doing this, and the proposal should be based -- this all is moot if the jury finds no violation of the UTPA. The question is going to be tomorrow, assuming the jury finds violation of the UTPA, what happens and assuming that I find that the claim -- and, again, I'm not remembering

the statute, but I'll call it the statute that deals with the penalties that might occur for the State, not as a consumer of the product, where they have to show ascertainable loss, but as a -- as the enforcer of the UTPA on behalf of the citizens of the State of Alaska.

What do we do about determining -- what does the jury need to determine -- this is the question I originally made. Do they determine something in that case or do I? And what would it be prudent, preserving everybody's objections and stuff, to have the State -- to have the jury decide because -- I'd rather have a record of the jury deciding something that maybe else said we didn't need to use this or the judge should have decided that or something else rather than not have that there and be told by the Supreme Court that we needed to have.

And so probably going to err on the side of even if I rule that this isn't a proper claim or those sort of things, I may want the jury to decide it so we don't have to retry this case if I'm wrong about that. And, again, I haven't even read either of your submissions other than that kind of briefly glance at Lilly's

there is an assertion that the second kind of claim the State is enforcing this on behalf of its citizens, Lilly's position, as I understand it, that's not what the case is about. I think that's what your position is.

MR. LEHNER: You characterize it generally correct.

THE COURT: Just to front this all, part of the reason I ask it is because if we make those determinations and I decide that that kind of claim exists, I don't know if we have a damages claim on that part of the thing. I think I just decide where does this fall in the range and multiply it by the number of violations and that's your penalty. And the second part of the phase we definitely have a jury decision, in the first part of the phase, if there was 20 violations and it's $1,000 fine, that's $20,000 and I think that's just math at that point. But maybe that's why I asked the question in the first place. I'm not -- I want to give everybody a condition to let me know what they think and why. And so we'll take some time tomorrow morning before we bring in the jury to discuss this and I'll read the stuff tonight.

If there's nothing else, then, we'll be off record -- oh, actually?

If Lilly's -- are there issues about depositions that Lilly wants to play that I need to decide something about?

MR. LEHNER: We gave, I think, four or five transcripts. They may have issues. They include most of the things that we counterdesignated previously.

MR. ALLEN: You're talking about your case in chief? We're going to start looking at them --

THE COURT: If you're going to have problems, I want to give them the same ability to make the rulings so they can prepare their stuff --

MR. ALLEN: I will never ask to insert one of my things into their play. I will only ask that one side look at it to play about 45 seconds to two minutes, I promise you, they can go ahead and cut their tape and get it done.

MR. LEHNER: We need to say what he intends to use on cross-examination. If we have an objection, you need to rule on it.

MR. ALLEN: Yeah, I won't do that.

Cut your tape.

THE COURT: What you're saying is, I mean, these are all your questions anyway for the most part of those people.

MR. ALLEN: Yes, Your Honor. I'm saying they can cut their tape and they can have at it.

THE COURT: Then I'll see everybody in the morning.

THE CLERK: Please rise.

(Trial adjourned at 1:50 p.m.)

REPORTER'S CERTIFICATE

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

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

IN WITNESS WHEREOF, I have hereunto subscribed my hand and affixed my seal this 17th day of March, 2008.

_____

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