PHILADELPHIA COUNTY COURT OF COMMON PLEAS

TRIAL DIVISION

IN RE: RISPERDAL LITIGATION	:	
	:	
THIS APPLIES TO ALL CASES	:	March Term 2010
	:	Case No. 296

Toronto, Ontario, Canada

Friday, December 14, 2012

Videotaped Deposition of:

DR. DENIS DANEMAN

the witness, called for examination by counsel for the Plaintiffs, pursuant to notice and agreement, commencing at 9:20 a.m., at Toronto Court Reporters, 65 Queen Street West, Suite 1410, Toronto, before Virlana Kardash, RPR, CSR, Commissioner of Oaths, when were present on behalf of the respective parties:

APPEARANCES:

On behalf of the Plaintiffs:
CHRISTOPHER GOMEZ, Esquire
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On behalf of Defendant Janssen Ortho:
WILLIAM ESSIG, Esquire
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On behalf of Defendants Excerpta Medica and Elsevier Inc.:
M. TODD MOBLEY, Esquire
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Also present: Videographer P. Rodney Barnes

C O N T E N T S

E X H I B I T S
(Attached to Transcript)

P R O C E E D I N G S

VIDEOGRAPHER: Good morning. This is P. Rodney Barnes, legal videographer from Legal Video Services, in association with Toronto Court Reporters. We are going on the record on Friday, December 14, 2012, at the time indicated on the video, which is 9:20 a.m.

Here begins videotape No. 1 in the deposition of Dr. Denis Daneman, taken by the plaintiff, in the matter of In Re" Risperdal Litigation. March term 2010, case No. 296, pending in the Philadelphia County Court of Common Pleas, Trial Division, and being held at Toronto Court Reporters, 65 Queen Street West, suite 1410, Toronto, Ontario, Canada.

The court reporter is Virlana Kardash, RPR, CSR, from the firm Toronto Court Reporters. Counsel, please introduce yourselves and state whom you represent. Then the court reporter will swear in or affirm the witness.

MR. GOMEZ: Christopher Gomez for the plaintiffs.

MR. ESSIG: Bill Essig on behalf of the Janssen defendants.

MR. MOBLEY: Todd Mobley on behalf of

defendants Excerpta Medica and Elsevier Inc.
Whereupon,
DR. DENIS DANEMAN
was called as a witness and, having first been duly sworn, was examined and testified as follows:
EXAMINATION
BY MR. GOMEZ:
Q Good morning, Dr. Daneman.
A Good morning.
Q My name is Christopher Gomez. I represent a number of plaintiffs who have filed lawsuits in the Philadelphia County Court of Common Pleas against the manufacturers of Risperdal and a medical writing company named Excerpta Medica and Elsevier.
Are you familiar with that litigation in any way?
A I am.
Q Okay. We're going to talk about that a little bit later, but before we begin, if you need to take a break at any time, please let me know, and we'll be sure to accommodate you. Have you ever been deposed before?
A I have.
Q I won't spend too much time then, but I just want to go over a few ground rules. I'll be

asking the questions, and you'll be giving the answers. Do you understand that?
A I do.
Q If at any time you don't understand my question or you want me to rephrase my question, will you let me know?
A Absolutely.
Q So if you do answer my questions, I'm going to assume you understood them and have given your best answer; is that fair?
A Yes.
Q We need to keep our answers yes or no, no nodding of the heads or saying "uh-huh" or "unh-unh" so the court reporter can get that down. Can you try to do that?
A Yes.
Q Okay. Dr. Daneman, what type of doctor are you?
A I'm a pediatrician and a pediatric endocrinologist.
Q What is a pediatric endocrinologist?
A So to become a pediatric endocrinologist, you have to have completed your training in pediatrics after medical school -- in Canada, you're Royal College certified or, in the U.S., board certified in

pediatrics -- and then do a period of training in a subspecialty called Pediatric Endocrinology, which basically deals with the hormone conditions of the body.
So there would be two or three major groups. Diabetes in childhood would be one major group. Calcium and bone problems would be a second major group, and then general endocrine problems would be the third major group.
Q Okay. We're in Toronto, Canada?
A Yes.
Q How long have you worked in Toronto?
A In my present situation, since 1981.
Q And if you don't mind, give me your present title and where you work.
A I work at the Hospital for Sick Children and the University of Toronto in the Department of Pediatrics where I'm currently Professor and Chair of the department of Pediatrics at the University of Toronto and Pediatrician in Chief at the Hospital for Sick Children.
MR. ESSIG: Doctor, if I may, you may want to take your time. It's going to be hard for our court reporter.
THE COURT REPORTER: Slow down. Thank you.

BY MR. GOMEZ:
Q Dr. Daneman, you kindly provided me with your curriculum vitae, which is numerous pages. Would it be fair to say -- and I'm generalizing. So tell me if I really am, but one of your main focuses of your practice and your career has been in pediatric diabetes; is that a fair assessment?
A Yes.
Q Have you ever written any journal articles in concert with the Janssen Pharmaceutical companies on that issue?
A On diabetes?
Q Yes.
A No.
Q We're going to get into it in more detail, but one of the main things we're going to talk about today is an article that was published in 2003 that you were one of the authors of.
A Yes.
Q Are you familiar with that article?
A Yes.
Q When was the last time you read that article?
A I suspect this morning.
Q Did you read the published manuscript?

A Yes.
Q I'm going to be showing you a number of documents today and asking you questions about them, but the first thing I'm going to do and mark as an exhibit is a document that you brought today which is a two-page document entitled "Denis Daneman Comments on Prolactin."
Let me just mark that as Exhibit 1.
(Whereupon, Exhibit No. 1 was marked for identification.)
MR. ESSIG: Chris, were you planning on marking the curriculum vitae as well? I have a copy if you want to mark that.
MR. GOMEZ: Yes. Remind me to do that as well. I'll do it right after this. I'm not going to ask him any questions about it, but we might as well put it on the record.
BY MR. GOMEZ:
Q Doctor, I'm going to hand you what I've marked as Exhibit 1. And if you wouldn't mind handing your copy there to Mr. Essig so I'll have one to ask you questions about. Doctor, prior to this deposition, did you receive a request in writing or any other way to produce certain documents in preparation for your deposition today?

A I did. I did.
Q Is this one of those documents?
A I produced what I had, and then I found one more document, and this was it. So that's why I produced it today.
Q Okay. And this is entitled "Denis Daneman Comments on Prolactin." Do you see that at the top?
A Yes.
Q When did you write this?
A I can't give you an exact date, but prior to the publication of that article, I put together some thoughts on how one would go about looking at the effect of prolactin on the body if you will.
Q The effects of the prolactin on the body, would that be specifically as to children and adolescents?
A Yes. I have no experience in adult.
Q Did you do this on your own, or did someone ask you to do this, to write this?
A I did this as a way of thinking through how we should analyze the data that came up in the Janssen Ortho Risperdal studies.
Q After you wrote this up, did you send it to anybody?
A I cannot recall.

Q Just so the jury understand -- and this is on videotape. So there's a high likelihood the jury will see this deposition -- can you tell them what prolactin is?
A Prolactin is a hormone that is secreted by the anterior part of the pituitary gland, and its main function is to support lactation in the woman who has just given birth to a baby. That's the lactin part of it. It stimulates the lactotrophs in the breast to produce milk. That's its major role.
Q Okay. And the first No. 1 here is the segmentation of prolactin levels. What does that mean?
A I tried at this time when I put this together to determine from the literature if there was a level of prolactin that had clinical significance. And this is the best I could come up with. Levels above 200 usually are associated with a tumor in the pituitary gland in which the lactotrophs -- those are the cells that produce prolactin -- form a tumor and produce prolactin in an uncontrolled manner.
And you usually have levels above 200. And that might be associated with a whole variety of side effects, not at all common in the pediatric population under 18. Much more common in the adult population.

My reading of the literature at the time was that in the 100 to 200 range, it was usually clinically important that below 100 it was difficult to be sure of what the importance was. And below 30, I couldn't find evidence that it was clinically important.
Then I made the comment that levels can be influenced by stress, usually not above 50, although we have seen them occasionally above 50. And I wondered for the purposes of the Janssen Ortho Risperdal studies whether we should segment into tertiles according to available data or else below the upper limits of normal, 25 to 30, in the 30 to 50, and above 50 range to see if -- the problem is that this is not a binary or ternary thing.
It's a constant. It doesn't go from 25 to 50 and then to 150. So this was just my thinking aloud.
Q When you're talking about these levels, is this a one-time level? Or is this -- did you take into account prolonged use and prolonged prolactin elevation at these different --
A So --
Q I'm sorry. Let me finish my question. It's just easier for the court reporter. The length of time that somebody has elevated prolactin levels,

did you take that into account or do a search on that issue?

MR. ESSIG: Objection to the form.

BY MR. GOMEZ:

Q You can answer.

A So if you go down to No. 4, relationship of level to side effects, my assessment from the literature I read was that the higher the level, the more likely -- my spelling there is incorrect I notice now.

The higher the level of prolactin, the more likely the side effects. But the duration was very important as well. Although I cannot recall finding anything to suggest what the duration exactly was that required attention.

Q You say the higher the level equals more likely; that's what you wrote here?

A More likely side effects. So above 200 more likely than below 100.

Q And when you say "side effects," what are we talking about?

A So what prolactin does besides in the woman who's just given birth to a baby and has an estrogen primed ductular system in the breast, it stimulates production of milk in the breast. That's the effect

of prolactin.

In somebody who's not just had a baby, high prolactin levels can in females -- and this is under No. 2 -- delay puberty, cause menstrual disturbances, amenorrhea, or loss of menstrual cycles, decrease in the number of menstrual cycles, menorrhagia, which is increased bleeding during menstrual cycles, infertility and galactorrhea.

Galactorrhea is production of milk from the male or female breast at a time that they're not pregnant or lactating. In the male, it can cause hypergonadism, which is underactivity of the testicles, gynecomastia, which is male breast development.

And in brackets I put there it's often fatty tissue rather than true gynecomastia. Galactorrhea is much less common in the male than the female. It can delay puberty. And there have been occasional case reports of high prolactin levels interfering with growth.

But that's very, very unusual and I don't think holds up. There's also some question as to the effect of long-term high prolactin levels on bone mineral density and also on sexual function, libido, sexual desire and function as well.

Q Let me back up and follow up on gynecomastia. That is breast growth in males; is that right?

A Yes.

Q That's how it's defined?

A Yes.

Q You say it's usually fatty. What do you mean by that?

A So in many males who are a little overweight, there can be fatty tissue in the breast region, and we call that pseudogynecomastia. True gynecomastia is when the duct tissue of the breast is actually enlarged.

You can have both together. You can have one or the other.

Q When you say that one of the side effects of prolactin is gynecomastia -- correct -- is that what you wrote here?

A I wrote that. It can be.

Q Is one of the side effects of prolactin fatty gynecomastia?

A So the more fatty tissue in the breast, the more likely the testosterone to estrogen conversion that I believe is the spirit in which that's written. Although I can't go back 12 years or so and tell you

exactly why that's there.

Q Would it be fair to say that true gynecomastia is usually evidenced by some sort of breast tissue?

A Yes.

Q And that can be seen or palpated by a doctor?

A Yes. Yes.

Q Going back to the segmentation of prolactin levels, if you have a prolactin level between 18 and 30 and it's prolonged, is the likelihood of side effects more prevalent?

A I have no evidence that it's prevalent at all. I have nothing in the literature that guides me on that nor clinical experience.

Q Under No. 5 you have value of Tanner staging. What did you mean when you wrote that, that title "Value of Tanner Staging"?

A Tanner staging gives you an idea of where the child that you're examining is on the continuum of prepuberty, early, mid, late puberty, and full sexual maturation. And if you're going to look at side effects of a medication on pubertal development, you need to know where they are in puberty to be able to make a comment on that.

Q Can a young man in puberty, ages 12 to 14, develop gynecomastia from prolactin elevation?
A It's a very good question, and the literature doesn't answer that with a definitive answer. The number of boys in the 12 to 14 year age group in puberty who have gynecomastia without elevation of prolactin is very high.
At some point in time, if you examine boys throughout puberty as they go through Tanner stages two, three, and up to four, up to two thirds of them will have some degree of breast tissue that develops and then regresses over time.
Q So if I understand you correctly, the fact that a boy is in puberty -- okay -- it's more likely that if he develops gynecomastia, it's from normal development through puberty?
A Pubertal gynecomastia, yes.
Q But -- strike that. Can a boy 12 to 14 in puberty develop gynecomastia from prolactin elevation caused by antipsychotics?
MR. ESSIG: Objection to the form.
THE WITNESS: I don't have a definitive answer to that from the medical literature.
BY MR. GOMEZ:
Q Based on your research and what you did

back before 2003, for example, in writing this up, can you categorically dismiss antipsychotic-induced prolactin elevation as a cause for gynecomastia in a boy in puberty?
MR. ESSIG: Object to the form.
THE WITNESS: How do I respond to the objection?
BY MR. GOMEZ:
Q You can answer. Did you understand my question?
A I don't understand the word "categorical" in the medical sense of the term. It requires me to give you a black and white answer, and the answer from the medical literature doesn't allow the answer to say categorically prolactin can cause it.
And one has to recognize that the medical literature stands at that point in time where the comments were made at that study, and it's free to be turned over by any subsequent studies. And I haven't seen anything in the literature since then that would categorically turn over the conclusions of that particular study.
Q Okay. Let me back up and just ask a general question. Okay? Are you familiar with Risperdal and what type of drug it is?

A Yes.
Q It's an atypical antipsychotic?
A Absolutely.
Q Is it your understanding that Risperdal raises prolactin? That's one of its side effects, so to speak?
A Yes.
Q And as a result of Risperdal raising prolactin, it can cause gynecomastia, generally?
MR. ESSIG: Object to the form.
THE WITNESS: It can.
BY MR. GOMEZ:
Q With what we just talked about right there and what you spoke earlier about puberty, if a boy between the ages of 12 and 14 develops gynecomastia, does the fact that he's in puberty eliminate all other causes of the gynecomastia?
MR. ESSIG: Object to the form.
THE WITNESS: So you'd have to have a significantly higher incidence of gynecomastia with the agent that you're talking about to be able to make a cause-and-effect relationship.
BY MR. GOMEZ:
Q If a doctor, an endocrinologist or any other doctor, is determining what caused a 12 to 14

year old boy's gynecomastia, can he dismiss out of hand every other cause just because that boy is in puberty?
A No.
MR. ESSIG: Objection to the form.
BY MR. GOMEZ:
Q We were talking about pubertal development in gynecomastia. You mentioned that the percentage is very high. Do you remember talking about that?
A Yes.
Q Where did you get that from?
A From the medical literature textbooks and over many years of experience of seeing hundreds of thousands of teenage boys. You know, you said earlier my major career is in pediatric diabetes. We see tons of teenage boys. We do the examination.
We stage their puberty. And a significant number of them develop gynecomastia during the early to mid stages of puberty.
Q Can you put a percentage on the percentage of boys in puberty between the ages of 12 and 14 who develop gynecomastia?
MR. ESSIG: Object to the form.
THE WITNESS: It's been said if you examine them carefully, up to two thirds would have some

evidence of gynecomastia.
BY MR. GOMEZ:
Q Are you referring to what they call the "Boyscout Study" or the study by Neidich(ph.) from 1961?
A I can't tell you who wrote the article. This came from Clinical Endocrinology and Metabolism some years ago. And I don't have the reference at my fingertips.
Q You can put that aside. I might come back to that. I'll take Mr. Essig up on his offer for a copy of your CV. I just want to put that on the record. Do you have a copy we can mark and the doctor can look at?
(Whereupon, Exhibit No. 2 was marked for identification.)
MR. ESSIG: Do you want me to give it to him?
MR. GOMEZ: That's fine. Let me just put a sticker on it.
BY MR. GOMEZ:
Q Doctor, I've marked as Exhibit 2 your curriculum vitae. You list -- in your CV you list by year the number of publications that you were an author on. Is that a fair assessment?

A Yes.
Q Did you list any posters?
A I haven't put any posters for a long time because there are just too many. I've left posters off for a long time because it got to be 200, 300 plus, and I just took them off my CV.
Q Fair enough. Let's go to page -- it doesn't have a page number, but 2003. It's about halfway through. Are you there?
A I opened it on that page.
Q Where the numbers under 2003 starts at 128?
A That's where I am.
Q Okay. On No. 131 --
A Yes.
Q It reads Findling R., Kusumaker V., Daneman D. -- that's you; correct?
A Correct.
Q Moshang T.?
A Yes.
Q DeSmedt G.?
A Yes.
Q Binder S. And it's entitled "Prolactin Levels During Long-term Risperidone Treatment in Children and Adolescents," The Journal of Clinical Psychiatry. Do you remember -- now that I've read

that, do you remember any specific posters from this article that were published earlier than 2003?
A There was one poster which is referred to in some of the information I gave you.
Q Okay. Now, who is Dr. Findling?
A Dr. Findling is a child psychiatrist in Cleveland who is a principal investigator of a number of studies of different medications in children with different types of psychiatric conditions.
Q When was the last time you spoke to Dr. Findling, if you remember?
A I spoke to him probably in the last six months.
Q Okay. Did you talk about this article at all?
A So Dr. Findling came as a potential candidate for a job interview at the University of Toronto and the Hospital for Sick Children. And I was interviewing him, and I mentioned that we had coauthored an article together.
And that's all we said.
Q Do you know where he currently works?
A At that time he was in Cleveland, and i believe he's still there.
Q Who is Dr. Or V. Kusumaker? Do you know

who that is?
A I believe he's a Canadian psychiatrist who's been part of these studies as well.
Q Do you know who Dr. Kusumaker worked for?
A No.
Q Do you know who Dr. Thomas Moshang is?
A Thomas Moshang was the Head of Pediatric Endocrinology of Children's Hospital of Philadelphia at the University of Pennsylvania at the time. He's since deceased.
Q Do you know Goedele DeSmedt?
A I do not.
Q Who is S. Binder?
A Carin Binder worked for Janssen Ortho at the time, and she was the one who coordinated the contributions that Tom Moshang and I made to this article.
Q It's Carin Binder, not "S. Binder"; is that fair?
A Yes. Correct.
Q Is Carin Binder a doctor?
A No.
Q What does she do?
A She worked in Janssen Ortho at the time, I believe, in clinical trials.

Q And Janssen Ortho is a Canadian company?
A I don't know where it's headquartered.
Q When was the last time you spoke to Carin Binder?
A About this study, probably there 2003, 2004. And I saw her once again at a meeting somewhere in the interim. I cannot recall where. We just said hello to each other, and that was it.
Q What was your understanding of the purpose of this medical article?
A So Risperidone was a relatively new treatment for these indications. You need to watch for two things. One is effectiveness or efficacy, and the other is the potential for side effects. And this was putting together of a number of studies that had been done in different places to see whether -- let me take a step back.
Q Sure.
A So any time you do a study, you have a primary outcome which is based on effectiveness, and you have secondary outcomes, which can be secondary effectiveness or side effects. And you may have the power to look at the primary outcome but not the power to look at the secondary outcome.
So putting together a number of studies and

looking for the secondary outcomes and the side effects may give you much more information than just looking at a single one.
Q And your role was to deal with the secondary outcomes that dealt with the safety issues?
A Specifically around prolactin.
Q Do you remember specifically when you were first contacted by Carin Binder?
A No.
Q Were you contacted by Carin Binder, or you were you contacted by Dr. Moshang?
A I can't remember talking to Tom Moshang at that time.
Q Do you recall when you first heard of the term or the acronym "SHAP"?
A As part of this study analysis.
Q That was the first time you heard of the acronym "SHAP"?
A Yes.
Q And SHAP is side effects hypothetically attributable to prolactin. That's one thing I've seen. Is that right?
A Yes.
Q Do you know where the term came from?
A No.

Q Let me -- sticking with your CV, going to, I think, No. 143. Are you there?
A I'm there.
Q And No. 143 is from the year 2004, and it's another journal article with the lead author of Dunbar F. or Fiona Dunbar; is that correct?
A Yes.
Q Did you meet before this article was published, or did you meet her after?
A Before this article was published.
Q And again, there's Dr. Kusumaker; do you see him?
A Yes.
Q And you're one of the listed authors there, D. Daneman; correct?
A Yes.
Q M. Schulz, who is that?
A Miklos Schulz is a biostatistician who's company did the biostatistical analysis of these data.
Q And Miklos Sculz is, as far as your understanding, a Janssen employee?
A No.
Q No?
A Not from my understanding at all.
Q Who does he work for?

A I thought he had his own private company that did biostatistical analysis.
Q And the title of this article was "Growth and Sexual Maturation during Long-Term Treatment with Risperidone"?
A Yes.
Q American Journal of Psychiatry. And it's published in 2004; correct?
A Yes.
Q What was your role in this publication? What were you asked to do?
A To review the data as they were produced.
Q You talked about looking at these articles. In your CV you've mentioned studies. Do you remember doing that?
A Yes.
MR. ESSIG: Object to form.
BY MR. GOMEZ:
Q Do you know what studies are you talking about?
A So in the first article, there were five studies, and the data were pooled from that. And the second article, the data came from those studies. I'd have to check directly to see which ones.
Q Do you know what type of studies they were?

A To the best of my knowledge, they were randomized control trials.
Q Have you ever heard of a study R-I-S-I-N-T 41?
A I don't know any studies by those titles. Can you give me the name of the study?
Q Sure. Do you remember -- I'm just trying to gather what you remember without looking at any documents. Do you remember an open label study?
A There was an open label study among them, yes.
Q What information were you given from those five studies?
A To the best of my knowledge, we were -- I was given -- and I suspect Tom Moshang was given the same thing -- a description of what the studies were and what the outcomes of those studies were.
Q Did you look at any of what they call clinical study reports?
A Those individual patient study reports?
Q Do you know what a clinical study report is?
A So are we talking about the individual patient, or are we talking about the group data?
Q I'm talking about the individual studies.

There was five of them. Correct?
A Yes.
Q Did you review any of the --
A I cannot recall that information.
Q Did you look at any of the underlying individual subject data for side effects?
A No.
Q What did you do to prepare for your deposition today?
A I took out what I had, and I read the articles that we'd written.
Q And the documents that you reviewed are the four documents that were attached to an email that you sent to Mr. Essig?
A I didn't go through those in any detail because those were the earlier drafts of the final component.
Q So in preparation for your deposition today, you didn't review any of the drafts?
A No.
Q Of the 2003 article?
A No.
Q I'm going to mark as an exhibit, as Exhibit 3, an email. Doctor, did you review this document in preparation for your deposition today?

A No.
(Whereupon, Exhibit No. 3 was marked for identification.)
BY MR. GOMEZ:
Q Could you take a moment and just briefly look it over before I ask you some questions. Are you finished?
A I am.
Q I'm going to specifically focus on the front page of the email that was from Carin Binder dated August 29, 2001. Do you see that there?
A I do.
Q And it's to numerous individuals; some are carbon copied. And the subject is "Prolactin Analysis." Did I read that right?
A Correct.
Q You're not listed as any of the recipients --
A Correct.
Q -- on this email; correct?
A Correct.
Q Do you know Ivo Caers?
A No.
Q Do you know who Rosanna Riccardelli is?
A No.

Q Do you know Albert Derivan?
A No.
Q After reading this email, does it refresh your recollection regarding a meeting that took place between Rosanna Riccardelli, Carin Binder, and yourself in 2001?
A I met with Carin Binder on more than one occasion, and sometimes there was somebody with her. I cannot recall the name of the person. So that name doesn't ring a bell. But what's discussed here is very similar to what's discussed in that document you labeled 1.
Q Okay. Okay. The document that you brought with you this morning?
A Yes.
Q Let me -- do you know what is referred to or what is meant by prolactin analysis?
A I presume the prolactin data in these studies.
Q Let me read the first paragraph of the email, and then I have a few questions for you. It says, "Dear All, a quick update regarding the prolactin analysis. Rosanna and I met with Dr. Denis Daneman, who is a peer of Dr. Tom Moshang and a pediatric endocrinologist."

"Our reasons for meeting with Dr. Daneman were to review the analysis plan and obtain additional validation that the areas Dr. Moshang wished to focus on had a broad appeal, not just to ped endos but to answer questions from pediatricians, GPs, et cetera."

Did I read that correctly?

A Correct.

Q Do you know what she meant when she wrote that she wanted additional validation that the areas Dr. Moshang wished to focus on. Do you know what she meant by that?

A I'd be presuming. I'd be speculating. My speculation was that she wanted to make sure that Tom Moshang was not missing anything and that it was as broad as you'd need to have recommendations for pediatricians and general practitioners who would be using this medication so they'd have as much information at their disposal as possible.

Q Do you remember in 2001 or at any time prior to your meetings with Ms. Binder and at those meetings a discussion on the issue of general practitioners or pediatricians having concern about Risperdal raising prolactin and causing side effects like gynecomastia?

A There was previously evidence that

prolactin -- that it was increased with Risperdal. And that's why this analysis was being formed. So that any side effects could be detected.

Q Do you remember any discussions that doctors treating children -- endocrinologists, general practitioners, pediatricians -- children on Risperdal were showing concern about prolactin-related side effects and were contacting the company to ask questions about that?

MR. ESSIG: Objection to the form and foundation.

BY MR. GOMEZ:

Q Do you recall anything like that?

A No.

Q She goes on to write, "Here is a synopsis of the conversation. And in parenthesis note Dr. Daneman signed a confidentiality agreement, was not involved in the P trials, nor does he know anyone that was involved."

Did I read that correctly?

A Correct.

Q Why were you asked to sign a confidentiality agreement?

A In dealing with data that's being analyzed and that doesn't belong to me, we always sign a

confidentiality agreement so that I don't have the right to go off and publish it somewhere else.

Q Okay. She goes on to write, "Firstly, Dr. D. felt that the prolactin elevation seen in the trials were not grossly abnormal." Do you remember what you reviewed to make that determination?

A I don't remember what the first data that we reviewed were.

Q Were you ever shown tables of statistics or tables of data combining all five studies?

A Yes.

Q Did you search for that prior to this deposition?

A I did.

Q You did not have it anymore?

A Didn't have it.

Q She goes on to write, "He stated that there was nothing in the literature or in guidelines to lead endos to create cutoff points except as follows: Less than 30, NG is okay. 30 to 100 is the gray zone. And greater than 100 is abnormal."

"And greater than 200, grossly abnormal." Did I read that correctly?

A Correct.

Q That's consistent with what we saw in

Exhibit 1?

A Yes.

Q "The important thing to consider is the height of prolactin elevation and the duration or elevation. The higher and longer the prolactin stays up, the more risk of sequelae." Did I read that correctly?

A Correct.

Q Is that -- at this point if you remember, was that your opinion, or did you learn that from the literature?

A That would have been my opinion, confirmed by the literature.

Q She goes on to write, "Dr. D. looked at the adverse events attributed to elevated prolactin, i.e. the 16 cases with gynecomastia, et cetera, and felt that these events might also be explained by reasons other than risperidone."

"For example, any boy going through puberty has a decrease in testosterone and an increase in estrogen. So it's not unusual to see some evidence of gynecomastia in boys aged 12 to 14 years." Did I read that correctly?

A Yes. But there's an error in how it's written. Any boy going through puberty has an

increase in testosterone, which is then converted to estrogen. So it's not a decrease in testosterone. It's an increase in testosterone and increase in estrogen.

Q Okay.

A So that statement --

Q So it should read, "Any boy going through puberty has an increase in testosterone and an increase in estrogen" is what it should say?

A Yes.

Q Okay. Okay. Do you remember what you looked at specifically as to the adverse events attributed to elevated prolactin, the 16 cases with gynecomastia, et cetera?

A I can't remember the exact documentation.

Q Do you remember looking at any Janssen documents that they gave to you which listed the adverse events in these studies along with the clinical investigators' determination of drug relationship?

MR. ESSIG: Objection to form.

THE WITNESS: I remember being exposed to a number of different documents, but it's too long ago to remember the exact nature of those documents.

BY MR. GOMEZ:

Q Do you remember talking to any of the clinical investigators in these studies?

A I didn't talk to any.

Q You did not talk to any clinical investigators?

A Dr. Findling and Kusumaker were part of a discussion right towards the end of the analysis.

Q But you never spoke to any of the clinical investigators that were at the different sites that the studies took place?

A No. No.

Q Did you ever look at any of the specific adverse event reports for each of these 16 cases?

A As I said before, I was exposed to some information on each of these cases. I cannot remember the exact nature of the documents that I saw.

Q It says here that you felt that these events may also be explained by reasons other than Risperdal; do you see that?

A Yes. Front page.

Q Do you remember if you were asked to provide an alternative explanation for the causes of these 16 cases of gynecomastia, et cetera, other than risperidone?

A There was always a discussion of gynecomastia as part of the normal pubertal development. That was the major one that reoccurred.

Q Did anybody ever come to you and say, "Dr. Daneman, here's some data. We have some clinical studies where we've seen these adverse events attributed to elevated prolactin, 16 cases of gynecomastia, et cetera"?

"Is there any other explanation for this besides Risperdal treatment?"

MR. ESSIG: Objection to the form.

THE WITNESS: I do recall talking to Tom Moshang at a meeting and discussing how best to look at a situation where you had a high frequency of gynecomastia in a group, and you had an intervention which potentially could cause gynecomastia, which is how I believe that SHAP A and SHAP B came into being.

BY MR. GOMEZ:

Q Now, we talked about that there were five studies; correct?

A Yes.

Q Were you aware that these 16 cases of gynecomastia, et cetera, came from one study?

A No.

Q Is that the first time you've heard that?

A I have no recollection of that whatsoever.

Q If you could go to the second page of this email, Ms. Binder writes, "Dr. D stated it is not common to see galactorrhea due to hyperprolactinemia unless estrogen is present. Dr. D also stated that brain-damaged children have early puberty, that hyperprolactinemia may delay puberty, and rapid weight gain to the point of obesity may induce puberty."

Did I read that correctly?

A Yes.

Q What did you mean -- I'm sorry. Strike that. What is Ms. Binder talking about when she says you stated that brain-damaged children have early puberty? And specifically, what do you mean by "brain-damaged children"?

A I'm not sure that that's my direct quote. But children who have sustained a significant trauma or insult to the brain can have a disruption in the hypothalamic pituitary gonadal axis function. And throughout prepuberty it's chronically suppressed.

And then something happens in puberty where it starts to be less suppressed and goes into puberty. And that chronic suppression pre-puberty can be taken off earlier. So children who had significant, for example, hypoxic ischemic damage in the newborn period

may be more likely to have early puberty than if they didn't have that.
Q Going down into the email, it says, "In general, he agreed with the analysis outline." Do you remember ever being provided an analysis outline?
A I can't recall whether it was, but there was a discussion of how the data were going to be analyzed.
Q She goes on to write, "If we don't have a great deal of Tanner data, he recommended that we use age as a correlation, parenthesis, surrogate marker."
A Yes.
Q What does that mean?
A So ideally, you'd like to have -- you'd like to know when people are pubertal, which is called Tanner stage one. And then as they go into early puberty, Tanner stage two, three. And then advanced puberty, four, five, which is sexual maturation.
And there was someone who did measurement in the U.K. and classified puberty along these lines. The problem with using age as a surrogate marker is you don't start -- everybody doesn't start puberty at age 10 and reach level three at age 12.
There's a spectrum. So boys start between say 10 and 14 years of age. And you'd expect a spectrum.

But if you don't have the Tanner staging, the next best thing is to look at age as the surrogate marker.
Q Okay. You can put that aside. This might be a good opportunity just to take a short break.
A Sure.
VIDEOGRAPHER: Going off the record at 10:12 a.m.
(Recess from 10:12 a.m. to 10:20 a.m.)
VIDEOGRAPHER: Going back on the record at 10:20 a.m.
BY MR. GOMEZ:
Q Dr. Daneman, before I mark our next exhibit, I wanted to follow up on one thing you said earlier. Correct me if I am wrong. Was it your understanding that this article was being written to seek some sort of pediatric indication?
MR. ESSIG: Objection to form and foundation.
THE WITNESS: My understanding was that my role was to comment on the prolactin levels and how they related to potential side effects. I wasn't informed as seeking of an indication.
BY MR. GOMEZ:
Q Were you aware that in 2001 time frame that Risperdal was not indicated to treat children in the

United States?
A I'm going to presume I was but probably more likely a Canadian indication than the U.S. indication.
Q Was there -- has Risperdal ever been indicated to treat children in Canada?
A I don't know the answer to that question, but there are many, many children who receive Risperdal on a regular basis.
Q Are you familiar with the term "off label prescription"?
A Yes.
Q What is that?
A So once a product, medication is approved for use for a specific indication, physicians can prescribe it for other indications very judiciously and carefully. And that's called off label.
Q When you say, "very judiciously and carefully," does that mean that physicians will look to sources of information for information to share with their patients regarding efficacy and safety, for example?
A Ideally, they should, yes.
Q One of the sources that physicians who prescribe drugs like Risperdal to an off-label

population like children and adolescents would be the medical literature; correct?
A Yes.
Q It would also be posters and abstracts that are shown at conventions; correct?
A Posters and abstracts at conventions would be sort of the lowest level of communication. It's really a communication to that band of people that is going to be at that meeting, which is often highly specialized small groups of people.
Q For example, there might be conferences of psychiatrists, for example?
A Yes.
Q You mentioned the lowest level of communication. Is there a secondary level or a top level?
A The top level is systematic reviews or meta analysis of many different studies, systematic reviews of the entire literature. Meta analysis means you take a whole lot of studies, and you review them together.
And then practice guidelines would come out from august bodies, national, international, sometimes local, but usually national, international, giving the guidelines for the treatment of certain conditions.

So that there would be if -- let's go back to diabetes. The American Diabetes Association has clinical practice guidelines. The Canadian Diabetes Association has clinical practice guidelines. Most of these are based, to some extent, on evidence-based medicine, which means the highest level of evidence.

The problem in the pediatric population is that there's only a certain amount of evidence to support what we do. And a lot of assumptions are made from the adult literature. So whenever we can get pediatric data, it's very important.

Q So it would be fair to say that a doctor who is deciding to prescribe Risperdal might look to the medical literature, specifically to the adult literature if no pediatric literature is present, for information on efficacy and safety; is that fair?

A Yes.

Q How would you characterize the article from 2003 that you were a coauthor on? Is that a meta analysis or top level of medical literature?

A No, it's an analysis of the available data. The ideal would be to have a single study in which enough patients were randomized to receive the drug versus not and treated for a long-enough period of time so that the primary outcome and the secondary

outcomes were reached.

That would be the strongest. This is a quite a lot down the line. And this is not a, you know, the American Academy of Pediatric Neurology or Pediatric Endocrinology that's giving an outcome. It's a group of people analyzing these studies.

So it's part of the process.

Q And as part of the -- strike that. And one of the reasons to draft articles like this and have them published is so prescribing physicians can be informed about any issues of efficacy and safety; is that fair?

A That's fair, yes.

Q And you would agree with me that medical literature like the article that we see that we're going to talk about more in detail and what we've seen so far should be done in an accurate manner; is that fair?

MR. ESSIG: Objection to the form. But go ahead.

THE WITNESS: Yes.

BY MR. GOMEZ:

Q And it should be in an objective manner as well; is that a fair statement?

A Yes.

Q And it should also be balanced?

A Well, there's a peer-review process that goes on in order to provide the checks and balances to those sorts of things. There are always individual interpretations for everything.

There's some things are that black and white which don't require any interpretation, but there are other things that are much more nuanced or shaded that are interpreted one way by the authors, and often the journals provide editorials, commentaries, and other things to provide counterbalance and so on.

Q According to your CV, you're a reviewer as well? You review journal articles; correct?

A Yes. Yes.

Q When you review journal articles, do you expect them to be balanced in terms of how they report the data, specifically safety data?

A Yes.

Q I've marked as Exhibit 4 a printout of an email from Mr. Essig to me regarding the documents that I asked you to, through my deposition notice, to go back and look for.

A Yes.

(Whereupon, Exhibit No. 4 was marked for identification.)

BY MR. GOMEZ:

Q And according to this -- and I have them all on this exhibit -- you provided four documents; is that fair?

A Yes.

Q The first two are February 19, 2003, revision. And I'm specifically referring to the attachments on the first page of the email. The first two are dealing with the 2004 article?

A Yes.

Q By Dunbar; is that correct?

A Yes.

Q And then we have the PRL. That's prolactin; correct?

A Yes.

Q That's revised July '03, final doc, and that's the 2003 article?

A Yes.

Q With Findling as the lead author; correct?

A Yes.

Q And then a prolactin ACAP abstract dated 2/13/02. And that is the abstract that was presented at ACAP on the 2003 Findling article; is that correct?

A Yes.

Q Now, before we go look at the article

itself and, specifically, the 2003 revised version that's attached to this email, did you specifically -- do you specifically remember what -- whether or not you wrote anything?

A I didn't write parts of the article. I commented on them. I can't give you exact detail as to which parts I commented on and suggested changes to, but I would have been -- I would have been an internal reviewer and commenting on the way in which it was written.

Q So it's fair to say somebody else wrote it?

A Yes.

Q And sent it to you for your comments?

A Yes.

Q And then incorporated your comments, and that was eventually the final product?

A Yes.

Q The published version?

A Yes.

Q Do you remember how many drafts you received?

A No.

Q Do you think the one attached to this email that you produced today was the only one you reviewed?

A I don't think it was the only one, but I

don't know the answer to that question. There would be a suggestion, to answer that question, on the articles which would tell you when they were reviewed, when they were received, when they were accepted.

Q Are you talking about the final article?

A Yes.

Q We'll take a look at that in a second. Do you remember who sent you these -- strike that. Do you remember who sent you the July 3 prolactin revision?

A My communication was with Carin Binder. So I would presume it was her. I can't recall receiving anything from anybody else.

Q We talked about the process, that somebody else wrote it, you reviewed it, added comments. Yet you still were listed as an author. That's something that's just normal and customary in the medical publishing world?

A So you would have -- you can see from my CV that there are sometimes many, many authors on an article. Somebody is the primary author, who writes the article, and the other people add their comments and criticisms and iterates until everybody is comfortable with it.

Q You mentioned in the email to Mr. Essig as

part of this exhibit that you wanted to get in touch with Carin Binder; do you see that down there?

A I did.

Q Did you get in touch with Carin Binder?

A No. No.

Q Okay. If you could go to the back and go forward until we find the last attachments which the 2003, July '03 draft. And let me know when you're there.

A I'm there.

MR. ESSIG: Chris, just so I'm clear, did I miss something or what shows that it's the July, 2003, draft?

MR. GOMEZ: Well, it was the attachment. If you look in the attachment email -- go to the front.

THE WITNESS: The attachment.

MR. GOMEZ: It says, "Attachment revised July 3, dot final doc."

MR. ESSIG: I see. Thank you.

BY MR. GOMEZ:

Q Doctor, where I have you looking at now, is that the July '03 attachment that we were talking about earlier?

A This is what that attachment is, yes.

Q Okay.

MR. ESSIG: Just so that we're clear, you're saying this document here is the document that was attached as labeled above here on the email as revised July '03?

MR. GOMEZ: That's correct.

MR. ESSIG: Okay. We're not saying that it's necessarily from July '03. We're just saying that's the name of the document?

MR. GOMEZ: That's the name of the document. That's fair.

MR. ESSIG: Okay.

BY MR. GOMEZ:

Q And Doctor, the title is "Prolactin Levels during Long-term Risperidone Treatment in Children and Adolescents"?

A Correct.

Q And the byline lists numerous authors, of which you're listed there, Denis Daneman, M.D., the Hospital for Sick Children, University of Toronto. Did I read that correctly?

A Correct; correct.

Q And along with Dr. Moshang, he's another pediatric endocrinologist that we've talked about earlier; correct?

A Since diseased, yes.
Q And Dr. Findling is a psychiatrist; correct?
A Yes.
Q And he's with the Case Western Reserve University in Cleveland, Ohio?
A Correct.
Q And Vivek Kusumaker M.D., she's or he's employed by J and J Pharmaceutical R&D, Titusville, New Jersey; correct?
A Yes.
Q And Goedele DeSmedt is also employed by J and J Pharmaceutical R&D out of Belgium?
A Yes.
Q And if you turn the page, Carin Binder, she's employed by Janssen Ortho here in Toronto, Canada; correct?
A Correct.
Q On that same page, page 2, special thanks to Miklos Schulz. We talked about him. He's the biostatistician?
A Yes.
Q Who's Ann Leung? L-E-U-N-G.
A Don't know.
Q Do you know Al Derivan? I think I asked

you that earlier.
A No.
Q And you know Dr. Fiona Dunbar; correct?
A Yes.
Q If we could turn the page to page 3. It reads under background -- and this is the abstract. What's an abstract?
A It's a one-page summary of everything that follows, a precis.
Q Why is there an abstract? Why not just have the article by itself when it's published?
A Two things. It allows it to be published on Medline, PubMed, or one of these places in this format without the whole article being there. And it also allows people to just skim the literature.
Q Going on what you just said there, this is one of the first places doctors go when reviewing a journal article?
MR. ESSIG: Objection to the form.
BY MR. GOMEZ:
Q Would you agree with that?
A Depends. If it's -- if you're looking for the meat of the article, you read the whole article. If you're looking for a quick fix, you look at the abstract.

Q So if a prescribing physician who's about to prescribe Risperdal to a child, an adolescent, and is concerned about side effects associated with prolactin, is one of the first places he's going to go is the abstract?
MR. ESSIG: Objection to the form. Calls for speculation.
THE WITNESS: I suspect the medical literature is not necessarily the first place they would go. The Compendium of Pharmaceutical Substances, the CPS, in the U. S. And in Canada it would --
BY MR. GOMEZ:
Q I'm sorry. I didn't mean to interrupt you.
A Where you can look at a whole lot of information about the drugs themselves without looking at the primary studies.
Q You're referring to like the package insert or the prescription drug label?
A Well, we get an updated book every year with all the pharmaceutical agents. And you can go through, and they list all the indications, the side effects, the dosing, situations that you need to --
Q That's published, I assume, in Canada every year like it is in the United States?

A Yes.
Q It's called the Physician's Desk Reference? PDR? Does that ring a bell?
A Yes. It's called the CPS in Canada.
Q That's one source where physicians can go to for information about safety and efficacy?
A So that's my first source because it's sitting right there.
Q Would the second source be medical literature?
A Yes. Medical literature would be a more in-depth source of information.
Q Okay. So if a doctor had specific questions about side effects related to prolactin elevation in Risperdal, that's what this article was designed to do, to answer those questions; is that fair?
MR. ESSIG: Objection to the form.
THE WITNESS: At least to ask those questions.
BY MR. GOMEZ:
Q Let's look at the background under the abstract. It reads, "This analysis was designed to investigate prolactin levels in children on long-term risperidone treatment and explore any relationship

with side effects hypothetically attributable to prolactin, SHAP."
Did I read that correctly?
A Yes.
Q So the main purpose of this article was to look at any relationship with Risperdal and things like gynecomastia; is that a fair assessment?
A Yes.
Q When it's written "any relationship," what does that mean?
A A cause-and-effect relationship.
Q Okay. When you're talking about relationship, are we talking about associations? Or are we talking about correlations?
A So you're talking about both. A study like this is not going to be definitive in its answer because it's only a certain dosing of Risperdal. It's only a certain duration. It's only a certain set of indications where it is.
This is not the final answer.
Q So is it true that certain tests or statistical tests were done to determine whether or not there was relationships, i.e. correlations or associations?
A Yes.

Q And if there was found to be an association, would we expect to see that in the body of the article?
A You'd expect to see it in the body of the article.
Q You would?
A If there was a relationship, yes.
Q Okay. What tests, if you know, are done to determine associations?
A Each set of data are going to be looked at in these cases by highly qualified biostatisticians who can give the best information in looking at these correlations with the correlation coefficients, the relationship between level and severity.
So if you can define severity as one, two, three, four, five and level as five, ten, 15, 20 and there's a nice straight line that fits, that would be the best correlation.
Q To test whether or not there was a correlation, you need to do a correlation coefficient test; is that correct?
A That's one of the ways of looking at it, yes.
Q And if you're going to determine if there's an association, you would do a test like a chi-square

analysis?
A Potentially, yes.
Q If you go down on this page to the conclusion, it reads, "With long-term risperidone treatment in children, serum prolactin levels tended to rise and peak within the first one to two months and then steadily declined to values within or very close to the normal range by three to five months."
Did I read that correctly?
A Correct.
Q Then it reads, "There was no relationship between the occurrence of SHAP extrapyramidal symptoms or improvement on the conduct problem subscale of the N-CBRF and prolactin elevation."
A Yes.
Q To break that down, that last sentence, would you agree with me that the reader can -- strike that. What is meant there is that the conclusion of this article was there was no relationship between the occurrence of SHAP and prolactin elevation; is that correct?
A Correct.
Q Let's go to page 7. The second paragraph, it reads, "There are no data in children as to the degree of prolactin elevation that warrants concern in

relationship to potential inhibition of growth, sexual development, or potential side effects such as gynecomastia or galactorrhea."
Did I read that correctly?
A Yes.
Q Okay. And that was your understanding as well back in 2001. There was nothing in the literature on this?
MR. ESSIG: Objection. Form and foundation. You just said 2001. I think we were talking about 2003 --
BY MR. GOMEZ:
Q Well, I'll rephrase the question. Back in 2001 when you were first contacted by Carin Binder, you were asked to look at --
A My clinical experience, my reading of the literature didn't give me the answers to that question.
Q Okay. And that's what that sentence is telling us as well; correct?
A Yes, yes.
Q It goes on to read, the article, "It is the experience of the authors," and in parenthesis, "pediatric endocrinologists TM and DD" -- that's Tom Moshang and Denis Daneman; correct?

A Correct.
Q "That prolactin levels above 18 but less, below 30 NG/ML, are rarely if ever associated with clinical manifestations or alterations of the hypothalamic pituitary gonadal axis"; did I read that correctly?
A Correct.
Q What does that mean?
A There's an area in the sentence, either less than 30 or below 30 is one of the other.
Q Is a prolactin level between 18 and 30 considered abnormal?
A So the normal range in males under 18 and normal females under 30 considered in the normal range. But it's been changing over time. And in our experience -- and it's still my experience to this day -- that levels under 30, in fact, probably under 15 are rarely if ever associated with any significant side effects.
Q And following up on that statement, "Prolonged elevations between 18 and 30 can lead to side effects." Is it more likely that they can lead to side effects based on a longer duration?
A I've never seen that.
Q Okay. The next paragraph reads, "The

objective of this post-hoc analysis was to investigate serum prolactin levels in children and adolescents with long-term risperidone treatment and to explore any possible correlation with side effects hypothetically attributable to elevated prolactin levels, SHAP."
Did I read that correctly?
A Correct.
Q What's a post-hoc analysis?
A This wasn't the primary analysis done at the time the original study was done. These studies were put together, and the data was done after the study was over.
Q So just so the jury understands, these five studies had already been completed?
A Yes.
Q And somebody made a decision to combine these five studies and do an analysis of the data and publish it?
A Yes.
Q Okay. What does it mean when it's written, "and to explore any possible correlation"? Are they talking about a correlation test? Or are they using the word interchangeably with "association"?
A So ten years after this was first written,

I can't give you the answer to that. It would be speculation.
Q Five minutes left on the tape. We might as well change the tape real quick. Let's do that.
MR. ESSIG: Sure.
VIDEOGRAPHER: This marks the end of videotape No. 1 in the deposition of Dr. Denis Daneman. Going off the record at 10:45 a.m.
(Discussion off the record.)
VIDEOGRAPHER: Here begins videotape No. 2 in the deposition of Dr. Denis Daneman. Going back on the record at 10:48 a.m.
BY MR. GOMEZ:
Q Dr. Daneman, we're looking at -- continuing to look at the July -- what's titled July '03. We'll call it a draft, that was attached to the email you produced in your deposition today. You and Dr. Moshang were asked to look at the adverse events possibly associated with prolactin elevation in risperidone; correct?
A Yes.
Q And you came up with -- was it your decision to or whose decision was it to come up with a SHAP A and a SHAP B?
A So we discussed for, I guess, at least a

significant period what it meant to have a patient who had gynecomastia at a time when pubertal gynecomastia was likely to be at its height. And we felt that there needed to be an analysis that included those children and excluded those children to see what the outcome was.
Q Can you define or do you remember before we look at this what the cutoff was in terms of age or SHAP A and SHAP B gynecomastia?
A I think we said 10 in boys.
Q Was there ever any discussion to include ages less than 10; do you remember?
A To include them?
Q As SHAP B.
A So those who are over 10 and had gynecomastia were excluded for SHAP B.
Q Right. Do you remember any discussion to make that age cutoff lower than age 10?
A I can't recall the exact nature of the discussion.
Q And why age 10 when there's discussions earlier that we saw regarding ages 12 to 14?
A Well, age 10, if you take Tanner stage two, nine to ten would be a gray zone. 10 to 13 and a half, to 14, actually 13 years and eight months, would

be Tanner stage two pubertal development in boys. That would be the range. So you wouldn't want to go much below 10.

Q I'm reading from page 13. It says, "An alternate definition of SHAP was used for the SHAP B population."

A Which one?

Q I'm looking at the bottom of page 13, second-to-last sentence. It says, "An alternate defense of SHAP was used for the SHAP B population."

A Yes.

Q So it's fair to say SHAP A was all inclusive of all ages in adverse events; correct?

A Yes, correct.

Q "SHAP B also excluded patients with amenorrhea less than one week in males 10 years of age or older with gynecomastia and females with less than 31 days of breast development." Did I read that right?

A Correct.

Q Then it's written, "It is considered normal for males to have gynecomastia at some point in the evolution of puberty, with the frequency estimated as high as 50 percent."

A Correct.

Q It goes on to read, "Adolescent gynecomastia" -- and when it says "adolescent gynecomastia," that means pubertal gynecomastia?

A Same thing.

Q May be unilateral, one-sided, or bilateral?

A Correct.

Q And occurs most frequently during stages three and four of puberty?

A Yes.

Q And lasts a few months to two years?

A Yes.

Q 27 percent in one series lasted a year, and 7 percent lasted two years?

A Yes.

Q Stages three and four of puberty, that's the equivalent of ages 12 to 14?

A Yes.

Q Why then are you excluding between the ages of 10 and 12?

A That's what our discussions led us to. I can't tell you 11 years later the reason for that.

Q So any children under the age of 10 who got gynecomastia, we can just all together exclude puberty as a cause?

A So if you have children who have gone into puberty who develop gynecomastia, males, the principle is that you have to investigate it very thoroughly to find a cause. It's going to very likely be a reason for it because males under the age of 10 don't produce enough estrogen to be converted to -- don't produce enough testosterone to be converted to estrogen in the peripheral tissues to allow the gynecomastia to develop.

Q Going through the rest of this article or this draft, if you could go to page 17, do you see where it says, "Insert table one"?

A Yes.

Q Do you remember seeing, prior to publication in 2003, any of the tables that were originally included in the final published article?

A I must have seen the tables.

Q If you had seen them, you would have reviewed them?

A I make that presumption.

Q Okay. Fair enough. If you go over to page 18, it reads, the top sentence, "The PA population." What is a PA population?

A I'd have to go back and look. PF often stands for primary analysis. But there must be somewhere where that is described.

Q Just for purposes of my question, I'll represent PA is primary analysis, so we can save some time.

A Okay.

Q And we'll see that later on in the final published article. But the sentence reads, "The PA population included 489 boys or 82.6 of the subjects in the PA population and 103 girls, 17.4 percent." Did I read that right?

A Correct.

Q What's the purpose of writing in the article the distinction between boys and girls and the number of each?

A There may be differences in the likelihood of complications, side effects in each.

Q You would want, for example, gynecomastia as something only seen in boys; correct?

A It's the equivalent of breast development in girls, yes.

Q However, if we're looking at gynecomastia, we only want to look at the boys. Is that one reason why the numbers are being put here; would you agree?

A That attribute is the only reason this was done. Gender differences are always put in papers.

Q And the purpose of an article like this is

to educate physicians or give them at least a source to go look for information about safety. And if you were having a prescriber who was concerned about side effects in girls, this is an article he could go to to get information about it; correct?

MR. ESSIG: Objection to form and foundation.

THE WITNESS: Correct.

BY MR. GOMEZ:

Q Did you say correct?

A I said correct.

Q Okay. If you could go to page 21. I'm sorry, Doctor. Please back up to page 20, if you could do that for me. There's a section called "Side effects hypothetically attributable to prolactin SHAP." Do you see that?

A Yes.

Q As we discussed earlier, it reads in the third sentence, "As such, two analysis were performed. The first analysis, SHAP A, used a more inclusive definition of SHAP. And the second analysis, SHAP B, excluded additional symptoms that the pediatric endocrinologist authors TM and DD attributed to puberty."

A Correct.

Q Okay. The second sentence reads,"Many children in this analysis were at the age of puberty. So the cause of SHAP could be uncertain." Did I read that right?

A You did.

Q So what the article is saying is we're going to do two analysis, one all inclusive, and one is excluding subjects based on age and so forth; is that right?

A Correct.

Q And you would expect the results of both analysis to be within the paper or the final published version; is that fair?

A Correct.

Q If you could go over to page 21, again the second paragraph under where it says, "Insert table 2." Do you see that?

A Yes.

Q It says, "The percentage of children with SHAP was assessed for SHAP B patients with prolactin levels above the upper limits of normal." That's "ULN"; correct?

A I'm on 21. Where am I looking? Okay. There we are.

Q Are you there?

A Yes.

Q I'll read it again. "The percentage of children with SHAP was assessed for SHAP B patients with prolactin levels above the ULN." That's upper limits of normal?

A Yes.

Q "Versus children with prolactin levels within the normal range at the various analysis time periods." Did I read that right?

A Yes.

Q Do you remember whether or not -- what was going on here is that they were at different time periods, weeks one to four, four to eight, et cetera, the comparison was being done of kids with elevated prolactin above normal versus children with normal prolactin levels.

And they were looking at whether or not there was a difference between those who suffered side effects; is that a fair assessment of what's being written there?

A It's a fair assessment, but I can't recall the discussion in any detail at all.

Q And what they're reporting here in the last sentence is that there was no statistical difference in the percentage of patients who reported SHAP for

any analysis time period whether or not prolactin levels were normal or above the upper limits of normal. Did I read that correctly?

A Correct.

Q Do you know what they mean when it's written here the authors, including yourself, in that last sentence we just read, when they're talking about SHAP, are they talking about SHAP A or SHAP B?

MR. ESSIG: Objection to the form.

THE WITNESS: I believe this is SHAP A.

BY MR. GOMEZ:

Q That's the all inclusive?

A I believe this is the all inclusive. I have to check the final table, yes.

Q Okay. But we can agree they did two separate analysis?

A Yes.

Q One on SHAP A and one on SHAP B?

A Yes.

Q Okay. And if you could go to page 24 under the discussion section. Are you there?

A I'm there.

Q If you look at the second paragraph beginning with "Only." Do you see that? "Only 13 of 592." Are you there?

A Yes.
Q It reads, "Only 13 of 592, 2.2 percent of children, develop symptoms hypothetically attributable to prolactin for SHAP, with nine out of the 13 children showing resolution of these symptoms at study end." Did I read that correctly?
A Yes.
Q Okay. The next sentence reads, "No correlation was found between SHAP and prolactin levels even when male gynecomastia during puberty was included." Did I read that right?
A Yes.
Q Is what the authors are trying to say here is that no correlation was found even in a SHAP A analysis; correct?
A Correct.
Q As well as the SHAP B analysis which excludes children over the sage of 10; correct?
A Correct.
Q And what sort of tests would they have done to determine whether or not there was a correlation?
A There were chi-squares, and there were correlation coefficients, as far as I can recall from reading the method section.
Q Based on your experience and your

knowledge, a chi-square test is for an association, not a correlation; correct?
A It's better for an association, yes.
Q Doctor, you can put that aside. Let me mark as Exhibit 5 the published version of the article we were just looking at. And I have a few questions about it.
(Whereupon, Exhibit No. 5 was marked for identification.)
BY MR. GOMEZ:
Q Dr. Daneman, I've put in front of you Exhibit 5, which is entitled "Prolactin Levels during Long-Term Risperidone Treatment in Children and Adolescents." That's the title; correct?
A Correct.
Q And this is the same authors that we saw on the draft; correct?
A Correct.
Q Is it fair to say that this is the final version of the --
A This is the published version.
Q -- of the draft we just looked at; correct?
A Correct.
Q Okay. And it was published in the Journal of Clinical Psychiatry in November, 2003?

A Correct.
Q Let's look over on the left-hand side between the two black lines. That's the abstract; correct?
A Correct.
Q And we looked at the background again. And again, the analysis was being designed to investigate prolactin levels in children and adolescents on long-term risperidone treatment and explore any relationships with side effects hypothetically attributed to the prolactin SHAP.
No change from the draft; right?
A Correct.
Q Okay. And under the "Results" section of the abstract, it reads, "At least one SHAP was reported by 13 of 592 children. There was no direct correlation between prolactin elevation and SHAP." Is that right?
A Correct.
Q Okay. When it reads, "At least one SHAP was reported by 13 out of 592 children," when they say SHAP, they mean SHAP A or SHAP B?
A This gives you the more conservative outcome, which would be -- let me just check -- SHAP B. This gives you at least -- this gives you the

minimum.
Q And then it says there was no direct correlation between prolactin elevation and SHAP?
A Yes.
Q Okay. Is there anything in the abstract that defines the difference between SHAP A and SHAP B?
A No.
Q So the reader of this article, if they were to go to the abstract, has no idea and would assume that SHAP was all inclusive?
MR. ESSIG: Objection to the form. Calls for speculation.
BY MR. GOMEZ:
Q Is that fair?
A I don't think the reader who goes to this would understand what the term SHAP meant. So by the time they finished reading the abstract, they would focus on the conclusions of the abstract.
Q Under the background, doesn't it define SHAP? So they could learn right from the background in the first paragraph what SHAP is.
A But that term would be relatively meaningless. What would be most meaningful in reading an abstract would be at the bottom in the "Conclusions."

Q Yes. What does it mean when the authors wrote, "There was no direct correlation between prolactin elevation and SHAP"?
A That you couldn't define at a certain level of prolactin that there would be a side effect of prolactin.
Q Specifically as to things like gynecomastia, that's the analysis we talked about earlier where they were looking at --
A Yes.
Q Those were the upper limits of normal versus normal and then looking at side effects to see if there was a difference?
A Yes.
Q If they had found a correlation, you would expect that to be here in the abstract as well as the article; correct?
A Correct.
Q Let's turn the page and go to the section under "Method." Are you there?
A I am there.
Q It says under here under "Pooled Study Databases" that five study databases of risperidone-treated children and adolescents were merged. "There were two six-week DB placebo control

trials." DB is double blind?
A Correct.
Q "With two 48-week OL extensions of those trials." Correct?
A Correct.
Q What's "OL"?
A Open label.
Q Okay. And then a stand-alone one year OL or open label trial to collect safety data; correct?
A Correct.
Q Were you aware that the one-year open label trial to collect safety data had over 500 subjects in it?
A Where is that? I went through the different study numbers at the time. I couldn't have quoted you today what the numbers were in each trial.
Q Okay. All I'm asking is, as you sit here today, are you aware that there was over 500 subjects alone in the stand-alone, one-year open label trial to collect safety data?
A Yes.
Q Were you aware that there were 24 cases of gynecomastia seen in that study?
A No.
Q Did you ever review the protocols of these

studies?
A I can't give an answer to that question. There was discussion of these protocols, and I can't remember whether I did or I didn't. It's too long ago to remember the details.
Q Let's break down the studies. There's two six-week studies; right?
A Yes.
Q Double-blind placebo control studies?
A Yes.
Q We can agree that those trials are not long enough to look for safety data?
A Absolutely.
Q Those are short-term trials; correct?
A But they can give you prolactin data.
Q Agreed.
A Yes.
Q But if we're looking at adverse events --
A Correct.
Q Okay.
MR. ESSIG: Object to the form, but go ahead.
BY MR. GOMEZ:
Q Let me ask the question again. The two six-week trials are not ideal to look at to determine

safety data or to gather safety data; correct?
A Correct.
Q And then we have two 48-week open label extensions of those trials. Is that a sufficient time frame to look at safety data?
A It's better than six weeks, and it's the best data we have, which is why it was reported. Is it the ideal way to do it? The ideal way is to have a double-blind placebo controlled, randomized trial that went for long enough to be able to be sure of that.
But that wasn't the case. So this is the best available, but it's not the best possible.
Q Okay. We can agree that the 48-week extensions are long term?
A Yes.
Q Are you aware of whether or not they paid special attention to side effects like gynecomastia in those open label extensions?
A My understanding is that there was attention paid to any potential side effects.
Q In comparison with the stand-alone, one-year open label extension, were you aware that in the protocols of that study that the particular special attention was paid to side effects like gynecomastia?

A I cannot recall the details.
Q Were you aware when you reviewed these five studies when physical exams were done to look for gynecomastia?
A We were -- I was aware of when the patients were seen.
Q And really the only way you can look for gynecomastia is to do a physical exam; correct?
A Correct.
Q Staying with the final article, can we turn the page. And under "Outcome Measures" on the right-hand side, if you go down to the third paragraph, you see there beginning with adverse events?
A Yes.
Q The first part of this paragraph talks about how the adverse events were looked at or how they were assessed; is that fair?
A Yes; correct.
Q Okay. The sentence beginning with "patients," it says, "Patients with SHAP were classified according to two sets of criteria, SHAP A and SHAP B."
A Correct.
Q So this is the article telling the reader

about the distinctions between SHAP A and SHAP B?
A Yes.
Q Okay. And then it's written down within the paragraph, "It is considered normal for males to have gynecomastia at some point in the evolution of puberty, with the frequency estimated as high as 50 percent"?
A Yes.
Q And that's consistent with the language we saw in the earlier draft; correct?
A Yes.
Q If you can go to page 1366 of the article, the page number is on the bottom right, Dr. Daneman.
A Yes.
Q This is where we see table 1 and figure 1. Do you see that?
A Correct.
Q Okay. And table 1 is describing the studies; do you see that?
A Yes.
Q And then what we talked about earlier, we see PA as primary analysis, and there's 592 -- correct -- in table 1; do you see that?
A Yes.
Q And then "ITT" is intent to treat?

A Correct.
Q Is that correct?
A Correct.
Q Okay. And then in figure 1, we have a chart or a graph entitled "Prolactin Levels in Children Receiving Long-Term Risperidone Treatment." Do you see that?
A Correct.
Q And then it has -- again, it's broken down by weeks. You see weeks four to seven there? That's where it's at the highest; is that right?
A Correct.
Q Then at weeks eight to 12, it's declined some way; right?
A Correct.
Q And then we see it declining over time all the way up through the end of weeks 40 to 48; is that what the graph is telling the reader?
A Correct.
Q If you go down to the section beginning "Side effects hypothetically attributed to prolactin"; do you see that?
A Yes.
Q It reads, "Many of the side effects hypothetically attributable to elevation in prolactin

levels are also commonly seen during puberty." Did I read that right?
A Correct.
Q You agree with that?
A Yes.
Q Okay. And then it reads, "Many of the children and adolescents in this analysis were at the age of puberty. So the cause of SHAP could be uncertain."
A Correct.
Q "As such, because of this, as such, two analysis were performed." Did I read that right?
A Correct.
Q Okay. And then it talks about the first analysis, SHAP A, used a more inclusive definition. And the second analysis, SHAP B, excluded additional symptoms based on, in the case of gynecomastia, age. Is that right?
A Yes.
Q Okay. And then if you go over to the next column -- okay -- you see the percentage of patients sentence there, three down from the top? Do you see that?
A First paragraph?
Q On the right-hand side.

A Yes.
Q Underneath table 4?
A Yes.
Q It reads, "The percentage of patients with SHAP was assessed for SHAP B patients with prolactin levels above the upper limits of normal versus patients with prolactin levels within the normal range at the various analysis time periods."
Did I read that correctly?
A Yes.
Q So that's talking about the SHAP B analysis; correct?
A Correct.
Q And when they compared kids with elevated prolactin with kids who didn't have elevated prolactin and they were looking at side effects to determine whether or not there was a relationship; is that fair?
A Correct.
Q Then it says, "There was no statistical difference" -- okay -- "in the percentage of patients who reported SHAP for any analysis time period." And then it reads, "whether or not prolactin levels were normal or above the upper limits of normal."
Did I read that correctly?
A Yes.

Q What's a statistical difference? What's that?
A Probability.
Q Is that where they do the chi-square test?
A Whatever statistical analysis is done will tell you if it's a P value less than whatever you've set for your study, that the probability of these two being different by chance alone is exceeded or not exceeded.
Q And if the P value is statistically significant, what does the reader learn from that?
A That the chances of having X, Y, or Z is greater than by chance alone.
Q In other words, if the P value is statistically significant, a reader could look at that and say kids with elevated prolactin have a higher propensity to develop SHAP throughout the trial; is that fair?
A You have to be a little careful in terms of statistical significance and clinically meaningful because sometimes the difference is tiny, but it reaches statistical significance. So you know, statistics are statistics.
They just give you the probability. They don't give you the impact of what's going on. And you have

to look at it in the raw data as well.
Q Okay. Again, the purpose -- I mean, we can agree the main purpose of this article is to talk about and look at any relationship?
A Yes, yes.
Q Okay. And if the relationship was found doing this comparison, you would expect to see it in the article; is that fair?
A Correct.
Q And we can agree what we just read was only the SHAP B analysis, which excludes kids over the age of 10; right?
A Yes.
Q Okay. Now, if we turn the page to 1368 under the discussion section -- are you there?
A I am there.
Q Let's go over to the right-hand column and then the second full paragraph or the first full paragraph beginning with, "Only 13 of 592." Are you there?
A Yes, I am there.
Q Okay. So the reader is going to this section in the discussion and would read, "Only 13 of 592, 2.2 percent of children and adolescents, develop symptoms hypothetically attributable to prolactin or

SHAP." Did I read that right?
A Correct.
Q "With nine of the 13 showing resolution of these symptoms at study end"?
A Yes.
Q No difference from what we saw in that draft we looked at earlier; correct?
A Yes.
Q It goes on, "No correlation was found between SHAP and prolactin levels even when male gynecomastia during puberty was included."
A Yes.
Q So that's an all inclusive. They're talking about the SHAP A analysis or everything; correct?
A Yes.
Q And they're telling the reader that they looked at that and they saw no correlation?
A Correct.
Q "This finding is in keeping with other studies in adults that also showed no correlation between prolactin levels and SHAP." So this analysis in this paper is reinforcing the adult analysis and reassuring the physician; correct?
A As one puts together ones discussion, one

looks at what there is in the literature and balances ones finding against that and then deals with the shortcomings of the particular study involved.

Q Now, in this final paper, if there had been an internal analysis done of SHAP A that showed a correlation, we would expect to see that in the paper; correct?

A You'd expect to see that in the paper, yes.

Q And we would also expect to see that, if statements are being made that there's no direct correlation between elevated prolactin levels and SHAP, that the type of test to determine whether or not there's a correlation would be in the paper; correct?

A Correct.

Q And if it's not possible to do a correlation test -- okay -- the statement of no correlation is kind of misleading; would you agree?

MR. ESSIG: Objection to the form.

THE WITNESS: It's not misleading if you read the last two paragraphs of the discussion, which clearly indicate the shortcomings of any analysis of this sort. The clinical implications of the study are many.

What clinicians can expect, it gives an accurate

assessment, and what the deficiencies are here. And so if you're a physician about to prescribe something, a medication in a situation, you're going to look at the conclusions more than you will look at correlation coefficient.

And it very clearly says, "Only a small percentage of children and adolescents treated with risperidone in this fashion will develop SHAP that requires intervention." And no matter what statistic you apply or not, that's something that holds very accurately.

BY MR. GOMEZ:

Q Okay. And that's within the article under that paragraph. But we can agree that, if you're going to do an analysis -- okay -- comparing children who had elevated prolactin and those who didn't and look at the relationship between prolactin and side effects, you want to be balanced and put in information that shows a correlation or shows an association?

A You want to put in the best available information.

Q Okay.

MR. ESSIG: Objection to form and foundation.

BY MR. GOMEZ:

Q I don't think you answered my question, though. You want to put in both sides for balance; is that fair? If you had information that showed an association or a correlation, you would want that in the paper?

MR. ESSIG: Objection.

THE WITNESS: Yes.

BY MR. GOMEZ:

Q If we can go back to page 1367, I want to specifically look at the tables. Why do you have -- what's the purpose of these, table 2 and table 3?

A To provide the actual numbers, to be able to look at them.

Q And when you say provide actual numbers, you're talking about the rates of side effects?

A Yes.

Q And prescribing physicians or anybody who reads the article, this is one place where they can go quickly to find that information; correct?

A The prescribing physician is very unlikely to go to the tables. He's much more likely to go to the conclusions.

Q Okay. But it's put in here for a reason. Hold on. Let me just finish my question. The reason

it's put in the article is to show the rates of side effects; correct?

A Yes.

Q Let's look at table 2. Under the PA or the primary analysis, we have a number of 592; do you see that?

A Correct.

Q Okay. And we saw earlier that 489 are males, and 103 are females. Do you remember that?

A I do.

Q That adds up to 592; correct?

A Yes.

Q Okay. So if you go down here where it says, "Reports of SHAP by preferred term," it says gynecomastia and says males; right?

A Correct.

Q Okay. And then you go over to the PA analysis, and it has 22. And I'll represent to you that 22 into 592 is 3.7 percent. That's what that's saying; correct?

A Correct.

Q Okay. If we're looking for gynecomastia in males, wouldn't we want the number under the PA to be 489 instead of 592?

A In looking at this in 2012, yes.

Q Okay. Do you think it's incorrect to measure or to put forth the percentage of gynecomastia in males and count females in the denominator?
A So when you don't count females in the denominator, the number changes from 3.7 to 4.5, I believe.
Q Something like that, yes.
A Something like that; yes?
Q Yes.
A And that's a very small differential. Ideally, you'd like to separate the two. It's a small differential.
Q It's not correct, though; agree?
A It's 22 of the 592 of both sexes. This is peer reviewed on more than one occasion and left to stand by erudite reviewers. So I'm not going to -- I'm not going to --
Q So the authors missed it and --
MR. ESSIG: Can you let him answer his question. He was almost done.
THE WITNESS: I'm not going to reject it on the basis of that.
BY MR. GOMEZ:
Q Okay. But we can agree that the reviewers missed it and the authors missed it? It would be

ideal to have 22 into 489 to get the true and accurate percentage rate for gynecomastia; you agree with that?
A Yes.
Q Okay. Now, you were talking about the difference between 4.5 and 3.7 is not significant, in your opinion; correct?
A You have to be careful about the word "significant." It's -- the probability of additional -- of a serious number of other patients developing it and changing the recommendations that come in the end of the paper is going to be very small indeed.
And I'll read those to you, if I may. "There's little justification for the discontinuation or reduction in dose of risperidone (INAUDIBLE) since the dose of risperidone did not (INAUDIBLE.) If a highly distressing hypothetically as attributable to prolactin" (INAUDIBLE) gives examples.
"Clinicians must balance the risk benefit ratio prescribing risperidone, especially in the face and the effect and outcome of untreated disruptive behavior disorder." That's a very balanced conclusion.
Q Okay. When we're talking about highly distressing side effects, is gynecomastia included

there, in your opinion?
A Galactorrhea and substantial breast enlargement, especially in males.
Q Let's look at the same table. Reproductive disorders in females. Do you see that?
A Going back? Yes.
Q And it says, "Eight reproductive disorders, adverse events, in females"; do you see that?
A Yes, I do.
Q They're delineated underneath that; correct?
A Correct.
Q It says 1.4. That's 1.4 percent; right?
A Correct.
Q And that's eight into 592?
A Or eight into 120, whatever the number.
Q Shouldn't it be eight into 103? That would be correct?
A I can't go back and tell you what the discussion was around it. I have no recollection.
Q Listen carefully to my question. I'm not asking about the discussion around it. I'm asking if you agree with me that it should be eight into 103. And that percentage, that would be correct?
A In 2012, if you put it that way, that's how

I would do the analysis.
Q Do you know whether or not anybody has ever taken any steps to correct these calculations?
A To provide a different analysis?
Q No. Has anybody -- do you know of anybody, authors, company representatives from Janssen, calling the Journal of Clinic Psychiatry and saying, "In our 2003 Findling article, we have some mathematical mistakes on the adverse event rates in females and males. We want to correct it"?
MR. ESSIG: Object to the form.
THE WITNESS: The term would be, "We have a different analysis" rather than an error.
BY MR. GOMEZ:
Q I'm specifically --
A I have no knowledge whatsoever.
Q As one of the authors, do you think maybe you might do that? Could you do that if you wanted, say to the journal that this needs to be corrected?
A Since I'm not the primary author -- Dr. Findling is -- I would discuss it with him.
Q You would discuss it with him first?
A Absolutely.
Q And then -- okay. Let's go down to table 3, which is SHAP B patients. Do you see that?

A Correct.
Q Now, we can agree when we looked at this earlier that what a table does is it gives you the number of subjects, the number of adverse events, and you get a percentage. And that's what we see in the table; correct?
A Correct.
Q Okay. Now, we can also agree that we looked at earlier the cutoff of age 10 --
A Correct.
Q -- in terms of gynecomastia; correct?
A Correct.
Q Okay. If you look at the number of patients with at least one SHAP -- do you see that?
A Yes.
Q Okay. It says 13 or 2.2 percent.
A Yes.
Q Now, do you agree with me that the 592 number is keeping in those male subjects over the age of 10 with gynecomastia?
A Both the tables are done with the same analyses, yes.
Q Okay. And if you look at the reports of SHAP by preferred terms, gynecomastia in males would have five cases or .8 percent; correct?

A Correct.
Q I'll represent to you that the number of males under the age of 10 is 255. If that's correct, assuming for purposes of my question, that should be the number for the denominator; would you agree?
A That's another way of doing the analysis, yes.
Q It is the more accurate manner to do the analysis; would you agree?
A It's a manner in which I would do it in 2012.
Q And again in table 3, we have the female analysis. Again, it's eight into 592 or 1.4. It should be eight into 103 in 2012; would you agree?
A I understand what you're saying.
Q Now, the readers of this article, if they went to this article and went to this table, are going to get a percentage of less than one of males developing gynecomastia under the age of 10 who are on Risperdal.
That's what they're going to glean from this table; correct?
A Yes.
Q If it was accurate and had 255 males, it would almost double; is that right?

A Yes.
Q You can put that aside.
MR. ESSIG: We've been going for about an hour. This is probably a good time for a break.
MR. GOMEZ: Sure. Short break.
VIDEOGRAPHER: Going off the record at 11:33 a.m.
(Recess from 11:33 a.m. to 11:41 a.m.)
VIDEOGRAPHER: Going back on the record at 11:41 a.m.
BY MR. GOMEZ:
Q Dr. Daneman, before we get into the next exhibit, have you reviewed in the course of getting ready for this deposition or at any time any of the expert reports in this case? By both sides?
A No.
Q No? Looking at Exhibit 6, it's an email and an attachment. Do you see that?
A I do.
(Whereupon, Exhibit No. 6 was marked for identification.)
BY MR. GOMEZ:
Q And it's from Carin Binder on Tuesday, July 16, 2002, to Gahan Pandina; do you see that?
A I do.

Q Do you know Dr. Pandina?
A No.
Q Have you ever met him?
A I'm unaware of that.
Q Do you know Vincent Nys?
A No.
Q In the subject is "Draft Prolactin Manuscript"; do you see that?
A I do.
Q And you're not on this email; correct?
A Correct.
Q It reads, "Hi Gahan, as promised. If there are glaring omissions, please let me know. Thanks, Karen." Do you see that?
A I do.
Q And then if we turn the page, it's the attachment; do you agree?
A I do.
Q Going down to the bottom left side, it says, "Revised July 16, 2002"; do you see that?
A I do.
Q It's entitled "Prolactin Levels in Children and Adolescents with Long-Term Risperidone Use"?
A Yes.
Q And again, the authors that are in the 2003

final published version that we just looked at in Exhibit 5; do you see that?
A Yes.
Q Do you remember seeing a July 16, 2002, draft of the final article?
A I saw drafts of the articles. I can't recall any one with a specific date.
Q If we go to -- I believe if you look on the right-hand corner, Doctor, there's a JJRE number; do you see that?
A Yes.
Q If you go to the JJRE number ending in 22 --
A Got it.
Q -- in the shaded portion, it reads, under the "Conclusion" section, "There was no direct correlation between prolactin elevation and the occurrence of SHAP, EPS, or efficacy." And then it says in parenthesis "Ann confirm." Do you see that?
A I do.
Q Do you know who Ann is?
A No.
Q If you could go to page ending in 33. Are you there?
A I'm there.

Q Okay. See the paragraph beginning "Patient demographics"?
A Yes.
Q Okay. It reads, "Patient demographics and pre-dose characteristics were compared between the PA and non-PA populations using the chi-square test for categorical data or T test for continuous data."
A Yes.
Q "The chi-square test was also used to compare the percentage of the patients who experience SHAP, EPS, or responders on the conduct problem subscale of the NCBRF in patients with a mean prolactin level above the upper limits of normal versus patients with a mean prolactin level within the normal range."
Did I read that correctly?
A Correct.
Q And what this is referring to is the type of test that was done to compare kids with prolactin above the upper limits of normal versus kids with normal prolactin in the studies that got adverse events like gynecomastia; am I right?
A Correct.
Q And the chi-square test is a test that would show an association; correct?

A Correct.
Q If I go do here, it says, "Correlation coefficients were calculated to assess correlation between prolactin levels and age and score on the conduct problem subscale of the NCBRF." And a correlation coefficient is a test for whether or not there's a correlation; correct?
A Correct.
Q If you could go to the page ending in -- page -- Bates stamp ending in the JJRE number and 40. Are you there?
A I'm there.
Q If you go down to the paragraph beginning with, "The percentage of children with SHAP." Do you see that?
A Yes.
Q It reads, "The percentage of children with SHAP was assessed for patients with prolactin levels above the ULN versus patients with prolactin levels within the normal range at the various analysis time periods."
Did I read that right?
A Yes.
Q "The proportions were all comparable except for the weeks eight to 12 time period, in which

7.8 percent of patients who had prolactin above the ULN had SHAP at some point during the trial, while 2.9 percent of patients with prolactin levels within the normal range at weeks eight to 12 experience SHAP at some time during the study. P is less than 0.02."
Do you remember seeing this, what we just read?
A No.
Q Is this the first time you've ever seen it?
A I can't answer that question.
Q What is being told to the reader, based on what we just read?
A It's a very complex sentence which most readers won't understand. In time period eight to 12 weeks, 7.8 percent of patients who had a high prolactin level had SHAP at some point during the trial, while 2.9 with normal levels also had SHAP. And there's a difference between these two.
This is a contortionist assessment.
Q Okay. You think this is a contortionist assessment, what we just read?
A It's very difficult to know what the relationship is between the SHAP and the timing of this elevation of prolactin and whether, at the time they had what's called a SHAP, they, in fact, had an elevation of prolactin.

So it's not a sentence that I would like to keep in a paper.

Q We can agree that what's being written here is the results of the chi-square analysis comparing children with prolactin levels above the upper limits of normal versus children with prolactin levels below the upper limits of normal.

And it's showing that kids with elevated prolactin had a much higher percentage or a higher percentage of side effects versus those with prolactin levels below the upper limits of normal; is that fair?

MR. ESSIG: Objection to form and foundation.

THE WITNESS: I don't think it's fair. My analysis here is the SHAP and the prolactin level are not comparable because they don't -- the statement there doesn't tell you that the complication occurred at the time that the prolactin level was higher.

BY MR. GOMEZ:

Q Okay. Do you remember when we looked at the chart of the prolactin level where it peaked at weeks four to eight and then eight to 12 at just below the peak level? So they were above the upper limits of normal at weeks eight to 12; is that correct?

A Yes. Yes.

Q Okay. The P is less than 0.02. Is that statistically significant?

A It is.

Q What does that mean?

A That the chance of finding this difference by chance alone is less than 2 percent.

Q And it's evidence of any type of relationship that --

A Yes.

Q -- that the paper was designed to look for; correct?

A Yes. But read the next sentence. "There was no statistical difference in the percentage of (INAUDIBLE) whether or not prolactin levels were normal or above." So it's difficult to know what one point in time means and the timing of the SHAP.

Q But we can agree, based on the prolactin level chart we looked at earlier -- we can go back and look at it. But at weeks 8 to 12, prolactin was just below the peak level and above the upper limits of normal; correct?

MR. ESSIG: Objection to form.

THE WITNESS: Correct.

BY MR. GOMEZ:

Q Okay. And that's where they found a

statistically significant association between elevated prolactin and SHAP for kids that went on to the rest of the study?

A Yes.

Q Is that fair? Is that a fair interpretation?

A That's fair. But they don't -- but those statistics don't tell you the relationship between the timing of the SHAP and the actual prolactin level at that time.

Q But if the analysis is looking at the relationship that we talked about at various analysis time periods, this is a relationship that was found at weeks eight to 12.

A Okay. So one has to be very careful in statistics at how you interpret them. When you do a huge number of statistical analyses in a study -- and there were a huge number done here -- something is going to come up that shows you relationships that may or may not exist.

Q I'm not trying to argue with you. I guess my question is this. That is an association that was found?

A Yes.

Q Correct?

A Correct.

Q Would you expect to see that in the final paper based on what you testified earlier about, that medical literature should be balanced?

MR. ESSIG: Objection to the form.

THE WITNESS: So a paper goes into a journal, and the editors of the journal send it out to reviewers. The reviewers make suggestions of what can be done, invariably decrease the length of the paper, suggest that certain things be taken out because they can't be substantiated.

And you revise the paper according to what they say. So sometimes the final article leaves out details that you would like to put in.

BY MR. GOMEZ:

Q So what you just testified there was total speculation. You don't know whether or not that was submitted to the journal, whether or not they told them -- the authors to take it out? You have no idea?

A No idea.

Q Okay. But what we do know is that there was an association found; correct?

A It is suggested by that.

Q And it was in July 16, 2002, draft of the article that was eventually published?

A Correct.
Q Correct? The draft that we looked at, which was entitled July, 2003, that was attached to the email that Mr. Essig sent me did not discuss that association; correct?
A Correct.
Q And in the final paper, there's no mention of it as well; correct?
A Correct.
Q And can we agree that the final paper said that the analysis at all the various analysis time periods of SHAP B showed no relationship? And even when kids with puberty were included, the same was found; is that correct?
A Correct.
Q Okay. And that's the complete opposite of what we see in this draft; correct?
MR. ESSIG: Objection to the form. And foundation.
BY MR. GOMEZ:
Q Correct?
A Correct.
Q Let's go to page Bates stamp ending in 41. Now, this was an attachment to a Carin Binder email; correct?

A Correct.
Q After the sentence that we just read in brackets, there's some comments. Do you see that, at the top?
A Correct.
Q It reads, "How do you want to handle the one significant value?" Do you agree that what she's asking about there or whoever wrote this is asking about is the significant value mentioned in the preceding sentence?
A I presume so, yes.
Q "The poster states there was no direct correlation with prolactin elevation in SHAP. What analysis was used for this?" Did I read that correctly?
A Correct.
Q We know, based on what we read earlier, that the chi-squared analysis was done to look for the relationship between elevated prolactin levels and SHAP; right? Yes?
A Correct.
Q Okay. "Can we get correlation coefficients for prolactin levels versus SHAP, as was done for prolactin levels versus age? And if no correlation, just stick with that." Did I read that correctly?

A Correct.
Q You would agree with me that you can't do a correlation coefficient for prolactin levels versus SHAP?
A You can do it. It has a different connotation.
Q Don't you need two continuous variables to do a correlation coefficient?
A You do.
Q If you're comparing prolactin levels versus SHAP, one of those is not a continuous variable; therefore, you cannot do a correlation coefficient. You would agree?
A Correct.
Q You can put that aside, Dr. Daneman. Thank you. I'm going to mark as Exhibit 7 another email and attachment, sir.
(Whereupon, Exhibit No. 7 was marked for identification.)
BY MR. GOMEZ:
Q Dr. Daneman, I've marked as Exhibit 7 another email and attachment. Do you see that in front of you?
A I do.
Q Okay. Let's take a moment and look at the

email before we go to the attachment. And this email is from at the top, again, somebody forwarding the pooled prolactin manuscript. And it's from Carmen Deloria; do you know who that is?
A No.
Q To Joseph Lynn; do you know him?
A No.
Q No?
A No.
Q Okay. They're forwarding an email from Dr. Pandina that was sent on August 21, 2002. Do you see that below?
A Yes.
Q Okay. And he was sending it to Carin Binder and Goedele DeSmedt, who was one of the authors or two of the authors of the 2003 article; correct?
A Correct.
Q And Magali Reyes-Harde, do you see her name?
A Yes.
Q Okay. And then Albert Derivan is carbon copied as well as Ivo Caers; do you see their names?
A I do.
Q And the subject again is the pooled prolactin manuscript; correct?

A Yes.
Q Okay. He writes, "Dear Team" -- before I read the email, you're not on this email, are you?
A No.
Q Okay. Do you ever -- let me read it. "Dear Team, attached please find my comments. I think the paper is overall constructed well and well written. I think we need to include the lack of association between Tanner height delay and prolactin level with SHAP, as our advisors tell us that this is one serious concern about prolactin."
"If we can demonstrate that the transient rise in prolactin does not result in abnormal maturation or SHAP, this would be most reassuring to clinicians. I realize that these manuscripts are being developed in parallel, but the relationship here is important."
Is he talking about the 2004 Dunbar article as well, if you know?
A I don't know. I would presume so.
Q "We have also had many concerns about patients who are maintained on stimulants, as this might affect prolactin level, and no subanalysis were included. Perhaps we can discuss prior to the next revision."
"Congratulations on the Tanner data being

accepted. Great news. Maybe this will make it easier for us to include this as a sub-analysis in this paper. Gahan." Did I read that right?
A You did.
Q Okay. Do you remember any discussion about one serious concern about prolactin was the levels in SHAP?
A No.
Q Do you know what he means when he said, "If we can demonstrate that the transient rise in prolactin does not result in SHAP, this would be most reassuring to clinicians"?
MR. ESSIG: Objection to the form. You just skipped the first part of that sentence.
BY MR. GOMEZ:
Q Fair enough. I'll read it again. Thank you, Bill. "If we can demonstrate that the transient rise in PRL does not result in abnormal maturation or SHAP, this will be most reassuring to clinicians." Do you know what he means when he writes that?
A So I have to attribute what I think he means to ten years and three months later. So you're okay with that?
Q Yes. Your best answer.
A So in that chi-square where you showed

that, if it's high at this eight to 12 week period, at some point in the later period, you may have SHAP. And if it's normal there, you would have one third or whatever -- 7.8 versus 2.9. And that was .02. Okay?
Q Right.
A And that's one of many investigations. And that doesn't give a sense of security that there's a good association or relationship in any way because you've got a point here and something there. So if you can demonstrate that there's normal physical maturation in patients receiving any medication, it would make the -- it would sort of smooth out those levels of prolactin.
Q When you say "physical maturation," you're talking about another analysis, though, that was the focus of the Dunbar paper that looked at the same five studies; correct?
A Abnormal maturation is what I would expect and that's what we mean, yes. Maybe I'm attributing too much information there.
Q My questions are focused solely on the relationship between SHAP and elevated prolactin levels.
A I don't think -- I would be attributing things that I'm not sure I can.

Q Sure. I don't want you to speculate. If the message of the paper was that there was no -- that prolactin rise is transient and not related to side effects hypothetically attributable to prolactin, does the significant value that we looked at in the previous draft fly in the face of that key message?
A It argues against the key message. It's not the whole story against it because of the timing and the relationship.
Q Understood. But it goes against the key message?
A Yes. Often in any multiple analyses that you're going to do, you're going to get intuitive and counterintuitive answers. And you have to deal with them.
Q If you have a significant value at weeks eight to 12 in looking at all SHAP, it also is in direct conflict with the statement that there was no direct correlation between prolactin levels and SHAP; is that fair?
MR. ESSIG: Objection to the form.
THE WITNESS: Yes.
BY MR. GOMEZ:
Q Let's go to the email from Carin Binder below that; do you see that?

A I do.
Q This is on August 15, 2002, and this again is to Goedele DeSmedt, who's one of the authors and a Janssen employee, as well as Gahan Pandina. Ms. Binder is actually an author as well. You're not on this email, are you?
A No.
Q Do you see her second paragraph? "Key Message. Prolactin rise is transient and not related to side effects hypothetically attributed to prolactin, EPS, or efficacy response"; do you see that?
A I do.
Q Okay. And on the second page of the email, she writes, "P.S. If this needs to be sent to other people to be reviewed, please forward." Do you see that?
A Yes.
Q Do you know if this was ever forwarded to you?
A No.
Q Okay. If we can go into the draft. Go to the first page. Are you there?
A Yes.
Q I'm sorry. I do that too fast sometimes.

Again, we can agree, if you look at the bottom, it's July 30th, 2002. The authors are all the same. We can agree it's another draft of the final article that was published in 2003?
A Yes.
Q Okay. In the interests of time, let me take you right back to Bates stamp ending in JJRE 192. Let me know when you're there, sir.
A I'm there.
Q Okay. Let me point your attention to the second or the first full paragraph beginning, "The percentage of children with SHAP." Okay? Do you see that?
A Yes.
Q This is the part of the analysis comparing elevated prolactin levels in SHAP; correct?
A Correct.
Q And it reads, "The percentage of children with SHAP was assessed for patients with prolactin levels above the upper limits of normal versus patients with prolactin levels within the normal range at the various analysis time periods."
Did I read that correctly?
A Correct.
Q It says, "The proportions were all

comparable except for weeks eight to 12 time period, in which 7.4 percent of patients who had prolactin above the upper limits of normal had SHAP at some point during the trial while 2.9 percent of patients with prolactin levels within the normal range at weeks eight to 12 experienced SHAP at some time during the study."
And it has the P factor of .02; correct?
A Correct.
Q And here is another comment, and it's attributed to Gahan Pandina, based on his name. Do you see that at the end of the comment?
A I do.
Q And he writes, "This may be notable as this could be seen to suggest that patients who show an initial rise during the peak period above upper limits of normal do have a higher propensity for SHAP. I think we need to discuss this somewhere in the manuscript."
What does he mean by a higher propensity for SHAP?
MR. ESSIG: Objection to the form.
BY MR. GOMEZ:
Q You can answer.
A I think he means a higher propensity for

SHAP.
Q What does that mean?
A A higher likelihood.
Q And then he wrote, "I think we need to discuss this somewhere in the manuscript"; correct?
A Correct.
Q Was this discussed in the final manuscript that we looked at?
A No.
Q Do you think it should have been?
A I don't know what was submitted to the journal and what they kept in and what they removed. So I don't know the answer to that question.
Q Based on -- in your opinion, as one of the authors, is this something that you would have liked to have seen in the manuscript in terms of being balanced?
MR. ESSIG: Objection to the form.
THE WITNESS: Nine-plus years later or ten-plus years later, probably.
BY MR. GOMEZ:
Q If you can go to Bates stamp ending in 196. Do you see the third -- second -- third full paragraph beginning, "As a post-hoc analysis"?
A I do.

Q It reads, "As a post-hoc analysis of pooled data, these results should be considered exploratory in nature. However, the fact that the initial rise in prolactin levels with risperidone was transient and subsided to normal values reduces the safety concerns regarding long-term treatment in children."

"This is reinforced by the lack of direct correlation between elevated prolactin levels in SHAP and EPS." That sentence, "This is reinforced by the lack of direct correlation," is that a correct statement?

A Well, there was an association between SHAP -- between prolactin levels at the peak eight to 12 week and SHAP some time along the way.

Q If he's saying here that a lack of direct correlation -- okay -- if he's specifically talking about correlation, it's not possible because the test is impossible to do; is that correct?

MR. ESSIG: Objection to the form. Calls for speculation.

THE WITNESS: So there's a statistical interpretation of the world "correlation."

BY MR. GOMEZ:

Q Let me rephrase the question, if you were done with your answer.

A Yes.

Q Maybe it was a poor question. The statement is made, "There was no direct correlation between elevated prolactin levels in SHAP." Correct?

A Correct.

Q Yet we can agree that a correlation coefficient is impossible to do for that analysis?

A Correct.

Q So the term that there's no direct correlation is not correct --

MR. ESSIG: Objection.

BY MR. GOMEZ:

Q -- unless the word is being used interchangeably with another word for relationship or association; is that fair?

MR. ESSIG: Objection to the form.

THE WITNESS: Fair.

BY MR. GOMEZ:

Q He goes on to write, "If possible, this would be the place to specifically mention or /discuss the lack of correlation between Tanner delay and prolactin level or SHAP. I believe that if we are unable to include this, it will hurt the overall impact of the paper."

Did I read that correctly?

A Correct.

Q Do you agree with that?

A I'd have to reflect on it a long period of time because it's the first time I'm seeing that.

Q When he means hurt the overall impact of the paper -- strike that. The purpose of the paper is to educate the medical community; correct?

A Correct.

Q Is the purpose of the paper to impact the number of sales for a drug?

A No.

MR. ESSIG: Objection to the form.

BY MR. GOMEZ:

Q Should it ever be the purpose of a medical paper?

A No.

Q So how could it hurt the overall impact of the paper if the statistically significant association at weeks eight to 12 was discussed in the final manuscript?

MR. ESSIG: Objection to the form. Foundation. Calls for speculation.

THE WITNESS: I'd have to speculate.

BY MR. GOMEZ:

Q Okay. Would doctors who saw that, if they

were concerned about the relationship between Risperdal's prolactin elevation and things like gynecomastia, be less likely to prescribe the drug if there was a direct correlation?

MR. ESSIG: Same objections.

THE WITNESS: Can I just have the final manuscript back for a second?

BY MR. GOMEZ:

Q Sure.

Can you read my question back. And see if you can answer it.

(The reporter read the record as requested.)

MR. ESSIG: Same objections.

BY MR. GOMEZ:

Q Can you answer that?

A So in the actual manuscript that's published, the last paragraphs are different from this. And they do warn about the deficiencies in the analysis in the long-term group with the control group --

Q Can you specifically point me where you're going to?

A 1168, last paragraph on the right-hand column.

Q Okay. Let me read that out loud.

A In the second last, "The clinical implications of the novel findings of this study are many. First, clinicians can expect that, in the vast majority of children and adolescents exposed to long-term therapy with risperidone in these doses" --
Q Slow down.
A -- "prolactin levels will be raised early in the treatment course but will revert to levels within normal limits, in some cases (INAUDIBLE) without change of dose. Furthermore, only a very small percentage of children and adolescents treated with risperidone in this fashion will develop SHAP that require intervention."
And at 7.8 and 2.9 percent, that's still a small percentage. So I don't think that the outcome says -- misleads in any way, shape, or form.
Q Stay on that page, Doctor. If you go up to the paragraph beginning, "Only 13 of 592."
A Yes.
Q The sentence reads, "No correlation was found between SHAP and prolactin levels even when male gynecomastia during puberty was included." Do you see that?
A I do.
Q And based on the drafts that we've looked

at, that is a completely untrue statement; you would agree?
MR. ESSIG: Objection to the form.
THE WITNESS: That's not directly according to the interpretations of the statistics we've discussed.
MR. GOMEZ: Can you read that back, that answer?
(The reporter read the record as requested.)
BY MR. GOMEZ:
Q So you would agree with me that that sentence that I just read, "No correlation was found between SHAP and prolactin levels even when male gynecomastia during puberty was included," is incorrect?
MR. ESSIG: Objection.
THE WITNESS: Is inaccurate.
MR. GOMEZ: Fair enough. Let's change the tape.
VIDEOGRAPHER: This marks the end of videotape No. 2 in the deposition of Dr. Denis Daneman. Going off the record at 12:14 p.m.
(Recess from 12:14 p.m. to 12:17 p.m.)
VIDEOGRAPHER: Here begins videotape No. 3 in the deposition of Dr. Denis Daneman. Going back on

the record at 12:17 p.m.
BY MR. GOMEZ:
Q Dr. Daneman, you just said that the statement that there was no direct correlation between elevated prolactin levels and SHAP was inaccurate; correct?
A Looking back from the vantage point we are at now.
Q Were you aware that Janssen in its communications with the United States Food and Drug Administration told them that and leading up to the approval for the treatments --
A I'm not aware of that.
MR. ESSIG: Objection to the form.
BY MR. GOMEZ:
Q Let me rephrase the question. Were you aware that Janssen, in the communications with the FDA leading up to the approval to treat the symptoms of irritability associated with autism, which was eventually approved in 2006, that Janssen told the FDA in August and December of 2005 that there was no direct correlation between elevated prolactin levels and SHAP?
MR. ESSIG: Objection. Form and foundation. Assumes facts.

THE WITNESS: I'm not aware of the submission to the FDA.
BY MR. GOMEZ:
Q If that statement relied on the same study, the same five studies that this article relies upon, it's still inaccurate; you would agree?
MR. ESSIG: Objection to the form.
THE WITNESS: It depends on the efficacy and side effect ratio that's present.
BY MR. GOMEZ:
Q Let me rephrase the question. The question is -- it's a hypothetical question. Assume for purposes of my hypothetical that the statement by Janssen to the FDA that there was no direct correlation between prolactin elevation and SHAP relied upon the same five studies that the 2003 Findling article relied upon, it would still be an inaccurate statement; would you agree?
MR. ESSIG: Objection to the form and foundation.
THE WITNESS: The statement is inaccurate.
BY MR. GOMEZ:
Q Thank you. Let me mark as Exhibit 8 a printout from the www.psychiatrist.com abstract dated November 27, 2012.

(Whereupon, Exhibit No. 8 was marked for identification.)
BY MR. GOMEZ:
Q I'll show that to you. Take a quick second and look at it.
MR. ESSIG: Take as long as you need, Doctor.
MR. GOMEZ: Yes. I didn't mean that, Bill. He can take as long as he wants.
MR. ESSIG: Okay.
THE WITNESS: Would you like me to comment on this?
BY MR. GOMEZ:
Q A quick question, and then I'd love to hear your comment. The Exhibit 8 that I just gave you is a, for lack of a better term, an abstract of the 2003 article that we've been talking about today; correct?
A Correct.
Q And the conclusion, again, is there was no direct correlation between prolactin elevations and SHAP; correct?
A It's not the conclusion again. It's the 2003 publication. This is not an updated publication. It will never be updated. This is the way it will sit for the rest of time in memorium. It's done. It's

finished.
Q Do you feel an obligation as a pediatric endocrinologist and an author of this page to correct the inaccurate statement --
MR. ESSIG: Objection to form.
MR. GOMEZ: I'm not done with my question.
MR. ESSIG: Sorry.
BY MR. GOMEZ:
Q -- that there was no direct correlation between prolactin elevations and SHAP?
A Sir, I felt an obligation all along to follow part of the literature in this area to see what would happen to it. And unless I've missed a huge amount, there's precious little that informs physicians since 2003.
And any paper that appears in the literature is merely a snapshot in time. I'm sure many people would change a sentence or two or an interpretation going back. But there is a long period of time, and the opportunity for observations of studies and things that suggest what's going on, and there's not a whole lot out there in the literature.
I think you're aware of that.
Q But you will agree with me that we don't want literature out there that's inaccurate; do you

agree?
MR. ESSIG: Objection to the form.
THE WITNESS: My suspicion is in many papers there are sentences that you would focus on.
BY MR. GOMEZ:
Q Sure. But we can agree that the purpose of that paper is to educate the medical community about any association or any relationship between elevated prolactin levels and SHAP; agree?
A Agree.
Q Okay. And we can also agree that the statement that there was no direct correlation between elevated prolactin levels and SHAP is inaccurate; agree?
MR. ESSIG: Objection to form. Objection. Asked and answered.
THE WITNESS: I'd have to state what I said before. It has a certain inaccuracy to it.
BY MR. GOMEZ:
Q You agree that it's inaccurate?
MR. ESSIG: Objection to the form. Objection. Asked and answered.
THE WITNESS: Yes.
BY MR. GOMEZ:
Q And this statement, "There's no direct

correlation" on Exhibit 8 is from 2012; correct?
A It's going to be there forever.
Q Does the drug company whose studies were the impetus for this paper and where three or two to three of the authors were company employees have an obligation to correct it?
MR. ESSIG: Objection to the form.
THE WITNESS: So when something is submitted to the FDA or Health Canada, there is a very careful analysis that's done by the in-house people that looks at a whole variety of different things, looks at the source documents, looks at a huge number of things, and turns down a huge variety of different pharmaceutical agents.
They didn't turn this down.
BY MR. GOMEZ:
Q Right. But were you aware that, in August -- in May of 2005, the FDA sent a non-approval level to Janssen on the autism indication and stated that all the information submitted to date was insufficient?
Were you aware of that?
MR. ESSIG: Objection. Form and foundation.
THE WITNESS: No.

BY MR. GOMEZ:
Q Were you aware that, within that same letter in May of 2005, the FDA specifically addressed or focused to Janssen their concerns with elevated prolactin and long-term sequelae? Were you aware of that?
A No.
MR. ESSIG: Objection to the form and the characterization of the letter.
BY MR. GOMEZ:
Q Were you aware that Janssen in response stated that, based on the review of the same five studies that we talked about here today, stated there was no direct correlation between elevated prolactin levels and SHAP?
MR. ESSIG: Objection to form.
THE WITNESS: I'm not aware of the format of the FDA submission.
BY MR. GOMEZ:
Q Sure. And we agree that the -- I asked you earlier the question or the statement to the FDA, if based on the same five studies, is inaccurate; correct?
A That statement is inaccurate.
Q Let me mark as Exhibit 9 an email sent to

you from Dr. Arlan Rosenbloom.
A Thank you.
(Whereupon, Exhibit No. 9 was marked for identification.)
MR. ESSIG: Do you have an extra copy?
MR. GOMEZ: I don't. Sorry. Do you want me to make copies?
MR. MOBLEY: Yes. Or can I see it.
MR. GOMEZ: Yes. Let's pass it down. Do you want to take a second?
MR. MOBLEY: Yes.
MR. ESSIG: This is 9?
MR. GOMEZ: I think so.
BY MR. GOMEZ:
Q Doctor, let me know when you're ready. I just have a few short questions.
A I'm ready any time.
Q Okay. Do you know Dr. Arlan Rosenbloom?
A For a long period of time.
Q Okay. He's a pediatric endocrinologist?
A He's a pediatric endocrinologist.
Q Were you aware that he was an expert witness for the plaintiffs in this litigation before you received that email?
A I can't recall if I was aware or not.

Q I believe you responded in your response that you were not at liberty -- I'm paraphrasing, of course. And correct me if I'm wrong.
A I said --
Q Why don't you read what you said.
A "Since the issues you raised are currently sub judice, I think the only prudent response to this at this time is to thank you for your email and to promise to reflect further on your comments."
Q My question is straightforward and simple. Do you have any comments now on what he wrote you?
A I find this to be an unprofessional behavior.
Q By Dr. Rosenbloom?
A Absolutely and completely.
Q Okay.
A Unprofessional to the extent that I think perhaps he should be reported to his local medical association for tampering with a witness.
Q Okay. Even if he had no knowledge that you were a witness?
A How would something arrive on a Monday morning or Sunday night at 11:00 when I'm going to be giving a deposition later the same week nine years after its publication? Please help me.

Q Are you implying that I asked him to send that to you?
A I'm implying that he must have had information that -- I'm not implying that you asked him to send it to me, but I'm implying that he must have known that I was a witness this week. I've written 300 articles.
I'm sure there are inaccuracies in more than one article. I haven't gotten comments nine years later.
Q Okay. Now that you have had a chance to read what he wrote, do you have anything to comment upon?
A His statement No. 1, "Reference is made to females with less than 31 days of breast enlargement, brackets, gynecomastia, end quotes, I cannot imagine that you and Tom read the final draft with this zinger."
We specifically put in the female with less than 31 days of breast development for a reason. And the "brackets, gynecomastia" was that breast development in the female is equal to the gynecomastia in the male. So that was perhaps not explicit enough.
We put it in because there are girls who go into puberty and have a sort of stuttering entry into puberty where they will have breast development on one

visit and not on the next. So if you have nothing, nothing, nothing, some breast development, nothing, nothing, nothing, that was what we wanted to exclude.
The mean height and weight, there was a long discussion about standard deviation scores. And this was not relevant to the discussion we had to date in large part. And the third is what we have discussed. And there are data looking at the long-term outcome.
And the data -- the further data do not answer the question once and for all.
Q Answer what question?
A The question of the relationship or correlation between SHAP and prolactin levels.
Q Is there anything else?
A He does believe that there's a strong correlation between gynecomastia and risperidone.
Q Do you disagree with that?
A I think, at most, there's a weak correlation or association.
Q But association or correlation nonetheless; correct?
A But it's quite weak. It's put in the balance of efficacy versus side effects.
Q When you say "efficacy," efficacy in treating what?

A Treating the issues that are being treated with the risperidone, which is not the side effects. It's the indications for its use.
Q What if risperidone is being prescribed for sleep? Does the benefits outweigh the risks?
MR. ESSIG: Objection. Form and foundation.
THE WITNESS: I have no comments on that use.
BY MR. GOMEZ:
Q What about autistic children?
A I'm not going to comment on that either.
Q But you just commented upon the efficacy versus the risks. Why won't you comment upon it when questioned with certain diagnoses?
A Well, there are certain written indications for its use. And I personally don't prescribe it at all. I've never written a prescription for risperidone in my life.
Q Have you ever written a prescription for any other atypical antipsychotic?
A No, I haven't.
Q Thanks for answering my questions.
A Thank you.
MR. ESSIG: Let's take a break. I want to regroup and sit over here.
MR. GOMEZ: Sure.
VIDEOGRAPHER: Going off the record at 12:31 p.m.
(Recess from 12:31 p.m. to 12:41 p.m.)
VIDEOGRAPHER: Going back on the record at 12:41 p.m.

EXAMINATION
BY MR. ESSIG:
Q Good afternoon, Dr. Daneman. My name is Bill Essig. I represent the Janssen defendants. And I was going to ask you some follow-up questions here from some of the things that Mr. Gomez has asked. One of the things I wanted to talk about with you was again the process by which the manuscript was prepared that led to the 2003 Findling article, as we've been calling it, about prolactin that we've talked about a lot today. Okay?
A Yes.
Q Okay. And we saw earlier that Carin Binder from Janssen in Canada had contacted you about reviewing data from five of the studies of Risperdal use in children with disruptive behavior disorder. That's the data that you reviewed; correct?
A Correct.

Q And Miklos Schulz is a statistician that was hired by Janssen, as you understand it, to pull data from those five studies and put together a data package relating to prolactin and side effects such as gynecomastia for you and Dr. Moshang and the other coauthors to review; is that your understanding?
A Correct.
Q Okay. And that occurred in the fall of 2001; is that right?
A The timing of it, I can't give you, but I think you get that from the email trail.
Q Okay. I'd like to hand you what we've marked as Exhibit 10 to your deposition. If you can take a minute to look at that, and when you'd ready to answer a question, let me know.
(Whereupon, Exhibit No. 10 was marked for identification.)
THE WITNESS: Okay.
BY MR. ESSIG:
Q So Dr. Daneman, you've now had a chance to review Exhibit 10. It's an email from January 23 of 2002 sent by Carin Binder; do you see that?
A Correct.
Q And the email went to a variety of people inside the Janssen organization. And do you see that

on the "To" line and the "cc:" line?
A I do.
Q Okay. And you were not a recipient of this email, were you?
A Correct.
Q And the subject here is prolactin expert meeting. And would it be fair to say that Exhibit 10, this email, is essentially a report by Carin Binder about what happened at the meeting about the prolactin data that was held in Toronto on January 22, 2002?
A Correct.
Q Okay. So this was an internal summary of what happened at the meeting; is that your understanding?
A Yes.
Q Okay.
MR. GOMEZ: Objection. Form.
BY MR. ESSIG:
Q And she writes, "A quick update on the prolactin expert meeting held in Toronto January 22, 2002. Attendees included two ped endos, T. Moshang and D. Daneman, and two psychs, B. Findling and V. Kusumaker."
First of all, Doctor, do you remember attending a meeting here in the Toronto area in January of 2002

with other physicians to discuss the prolactin data that ultimately was discussed in the Findling article?
A I do.
Q And in addition to the doctors listed -- well, first of all, do you remember these doctors being present at the meeting?
A I remember Tom Moshang because I've known of him for a long time, and this is the first time we've actually had opportunity to spend time together. And I know Kusumaker was there, and there were other people on the phone.
I can't remember Bob Findling being there in person.
Q But he was a participant in the meeting whether on the phone or in person?
A Yes.
Q And there were other people present at the meeting, presumably Carin Binder, because she wrote this summary?
A Yes.
Q Do you recall roughly how long this meeting took place -- how long the meeting lasted, rather?
A It started about 8:30 or 9:00 in the morning and, I think, went to just after lunchtime.
Q So fair to say, roughly four to six hours

spent in this meeting with these other physicians --
A Correct.
Q -- to discuss the data regarding prolactin from Janssen studies?
MR. GOMEZ: Objection to form.
THE WITNESS: Yes. I can't exactly say the length of it. I wouldn't put a limit to it.
BY MR. ESSIG:
Q Okay. And do you have an independent recollection of participating in the meeting?
A You mean of being there?
Q Yes.
A Yes.
Q And tell us what was discussed at the meeting in general, to the extent that you can recall?
MR. GOMEZ: Objection to form. You can answer.
THE WITNESS: I think the one thing that I remember the most is that Tom Moshang and I had to make sure that we were on the same wavelength in terms of thinking through different things because there was some girls in whom a breast development was reported at one point in time and not the visit before or the visit after.
And that couldn't be looked at as a side effect

because this sometimes happens with this intermittent type of puberty that occurs in some girls. And it was very difficult to evaluate what gynecomastia meant in pubertal boys because of the background frequency of pubertal gynecomastia.
And the discussion was that I think we both felt that the levels weren't within our level of experience to be associated with gynecomastia.
BY MR. ESSIG:
Q And although you've just said this was the first time you met Dr. Moshang in person, would it be fair to say were you familiar with his writing and his stature in the pediatric endocrinology community?
A Absolutely.
Q And Dr. Moshang was a well respected endocrinologist?
A Absolutely.
MR. GOMEZ: Objection to form.
BY MR. ESSIG:
Q And having reviewed the email here, is Karen Binder's summary of the meeting, at least as far as what's in the email, accurate as far as you recall?
MR. GOMEZ: Objection.
THE WITNESS: What she reports here is very similar to what I wrote on that document in essence to

myself, my sort of notes to self, that No. 1.
BY MR. ESSIG:
Q That was Exhibit No. 1. That's right. I'm sorry. And turning back to the email here and the action items. Do you see that about two thirds of the way down the page?
A I knew nothing about Brain Works being hired to write the manuscript.
Q Well, let me ask you a question first. I just wanted to make sure you were here. Did you get to action items?
A Yes.
Q So let me read what she wrote here. "The additional analysis plan has been written up and sent to all participants for review. Brain Works has been hired to write the manuscript on the results and write an abstract and poster for ACAP in October."
"Authors will include Moshang, Daneman, Findling, Kusumaker. To discuss inclusion of Janssen people as authors." Did I read that accurately?
A Yes.
Q Are you familiar with Brain Works?
A No.
Q And at the end of the meeting, I take it there was a decision among the group that it would be

worthwhile to disseminate this data to other physicians?
A Correct.
Q And the formats that were discussed were doing an abstract and poster for one of the child and adolescent psychiatry meetings; is that fair to say?
A Yes, because that is what actually was done.
Q Okay. And the other mode of disseminating this data was to prepare a manuscript which ultimately became the Findling article; is that right?
A Correct.
Q You can feel free to put that aside. I'd like to hand you what's been marked here as Exhibit 11 to your deposition, Doctor. You can take a moment to review it, and when you've looked at it, let me know. And I'll ask you a couple of questions.
(Whereupon, Exhibit No. 11 was marked for identification.)
THE WITNESS: Okay.
BY MR. ESSIG:
Q There's a two-page attachment here to the email; do you see that, Doctor?
A Okay.
Q So Doctor, Exhibit 11 on the first page, we

have an email message from Carin Binder, dated January 30, 2002; do you see that?
A I do -- the lower one, yes.
Q Yes. And in the "To" line, there's a list of several email addresses, and it includes your address there; do you see that?
A I do.
Q That's your email address?
A It is.
Q And we have other email addresses here for others involved in the manuscript, including the other authors such as Dr. Moshang, Dr. Findling, Dr. Kusumaker; do you see that?
A I do.
Q And the subject here is "Prolactin Analysis." Is that right?
A Correct.
Q And Carin Binder writes, "Dear All, thank you to the people who gave input into the analysis plan. Attached please find the final plan. Miklos and Ann, may I ask you to please proceed with the next analysis and contact me if you have any questions."
"We are looking to submit an abstract by February 15, 2002, and would appreciate if we could obtain some preliminary data, please." Do you see

that, Doctor?
A I do.
Q Do you remember getting this email at all?
A I remember the emails going back and forth. The specificity, no. But getting emails, yes.
Q But this is part of the process in which you and the other coauthors communicated about the data plan and the analysis that you were performing?
A Correct.
Q The next line, it writes, "Dr. Moshang and Daneman, would you please identify the categories of medications, e.g. psychostimulants, antidepressants, close parenthesis, which may influence prolactin. And Al Derivan will scan the patient listings to identify those medications."
Do you remember having any involvement in making this identification of these medications that might influence prolactin?
A I have no recollection.
Q Okay. Then the next two pages of the document here, Doctor, that's the data analysis plan that Carin Binder was referring to in the cover email; is that right?
A Correct.
Q And this basically discusses what data the

statisticians, Miklos Schulz and his associates, would pool from the Janssen clinical trial databases and how you would analyze that data; is that fair to say?
A Correct.
Q And the results of that analysis ultimately became part of the manuscript that you and the coauthors prepared; is that right?
A Yes.
MR. GOMEZ: Objection to form.
BY MR. ESSIG:
Q Okay. All right. Doctor, because you were involved in the data analysis that we've just talked about today, ultimately you agreed to be an author of what we are calling the Findling article; is that right?
A Correct.
Q And as a coauthor of this article, do these conclusions in the Findling article reflect your independent clinical judgment as a pediatric endocrinologist?
MR. GOMEZ: Objection to form.
THE WITNESS: Yes.
BY MR. ESSIG:
Q And I'm sorry. I'm done with that exhibit, if you want to put it aside.

A Okay.
Q Doctor, did anyone at Janssen, any personnel, whether a coauthor of the article or otherwise, ever ask you to make changes to the article that you did not agree with?
A No.
Q And did anyone at Janssen, whether a coauthor of the article or anyone else, ever try to change the article in any ways that you did not approve?
A Not that I can recall.
Q Okay. Doctor, would you have signed on to the Findling article as a coauthor if you did not agree with its analysis and conclusions?
A Sir, can I give a longer answer than yes or no?
Q Sure.
A So Miklos Schulz had worked at The Hospital for Sick Children, where I work, for some time, some years before. And I had a lot of respect for his abilities as a statistician. And I felt reassured that he was independent as a statistician in this process.
So if I thought that there was something that was untoward, I wouldn't have signed up for it.

Q And we've talked today about some issues with some of the statistical tables in the article that in 2012 you might -- you might have expressed differently; is that fair to say?
A Correct.
Q And aside from some of those issues that have been talked about earlier, do you still, as you sit here today, stand behind the conclusions of the Findling article?
MR. GOMEZ: Objection to form.
THE WITNESS: So in the nine years since the publication of that article, there's not been a lot of information in the literature. If something is going to come up as a serious complication, you would expect there to be a literature that develops because no one article changes the face of medicine indefinitely.
It's, if you will, held as fact or implication of fact for only as long as until the next article that's more definitive. And I have seen precious little in the way of articles that have come out on this topic.
BY MR. ESSIG:
Q Doctor, I'd like to hand you what we've marked as Exhibit 12 to your deposition. It's an

article from 2007 from the Journal of Biological Psychiatry, authored by Dr. George Anderson and others.
The title is "Effect of Short- and Long-term Risperidone Treatment on Prolactin Levels in Children with Autism."
(Whereupon, Exhibit No. 12 was marked for identification.)
BY MR. ESSIG:
Q If you want to take a moment to familiarize yourself with that.
A I've read this in the past.
Q That was my first question. Have you reviewed this article before?
A I have.
Q Okay. And Doctor, the Anderson article is a review of prolactin data from a study of Risperdal use in 101 children with autism that had symptoms of aggression, tantrums, or self-injurious behavior; is that right?
A Correct.
Q And this is a study run by psychiatrists and researchers at various universities and medical centers in the U.S. that was part of a group known as RUP. Are you familiar with that?

A I'm not familiar with RUP, but I know this was a multi-center study.
Q Okay. And the RUP group and this study is something that was funded by the National Institute of Mental Health in the U.S., not by Janssen; is that your understanding?
A That's my understanding.
Q And of the group of patients here, as they note in the method section, 30 of them actually were followed up after 22 months of Risperdal use; do you see that, Doctor?
A Where are you? Procedures? Yes, yes.
Q And the study measured prolactin in these patients on Risperdal and also assessed the patients for side effects such as gynecomastia, galactorrhea, and menstrual problems. Did you see that, Doctor, on page 547?
A I did.
Q Okay. And the authors wrote at the top of page 547, "These adverse effects were rated as absent in all subjects at all times, although it is possible that a drug-induced weight gain may have masked or obscured gynecomastia."
Did I read that correctly, Doctor?
A You did.

Q And does this mean that the RUP study, as reported here in the Anderson article, found no cases of gynecomastia in these subjects?
A Correct.
Q What is the clinical significance to you, Doctor, as a pediatric endocrinologist, of this study and this article in light of your earlier article on the Janssen data on prolactin and gynecomastia?
MR. GOMEZ: Objection to form.
THE WITNESS: It's almost identical.
BY MR. ESSIG:
Q Identical in what way, Doctor?
A Well, it reaches the conclusions that Risperdal treatment was associated with the two to four-fold mean increase in the (INAUDIBLE) with autism although these increases (INAUDIBLE.)
Q So --
A It doesn't answer definitively the question. Certainly it suggests a low order of side effects.
Q I just have a few more cleanup questions here, Doctor. All right. Doctor, I'd like to hand you what we've marked as Exhibit 13 to your deposition.
(Whereupon, Exhibit No. 13 was marked for identification.)

BY MR. ESSIG:
Q Dr. Daneman, can you tell us what Exhibit 13 is?
A It's an assessment of the pooled databases with respect to growth and sexual maturation and the evidence that was available. The analysis was done by Miklos Schulz on these databases. And I was involved in looking at the data that he had.
Q So this is a copy of an article from the American Journal of Psychiatry published in May of 2004 with the title of "Growth and Sexual Maturation During Long-Term Treatment with Risperidone." Is that accurate?
A Correct.
Q And the authors on this article are yourself, Miklos Schulz, the statistician; is that right?
A Yes.
Q And then Dr. Kusumaker and Fiona Dunbar from Janssen; is that right?
A Correct.
Q And we've heard a little bit about this study today, but would it be fair to say that this was a sort of a follow-on study from the earlier analysis

of the data that had been done as part of the effort that led to the Findling article?
MR. GOMEZ: Objection to form.
THE WITNESS: This is the growth data on those that had growth data available.
BY MR. ESSIG:
Q From the five studies that were discussed in the earlier article; right?
A Correct.
Q Okay. And Doctor, what was your conclusion in this article about the effects of long-term treatment of Risperdal on growth and sexual maturation?
A In these studies using these doses of risperidone, growth and sexual development appear to be normal.
Q And on the second page at the end of this article, Doctor, there's a listing here about the fact that this article had been presented as a poster in part in San Francisco in October of 2002 at the meeting of the American Academy of Child and Adolescent Psychiatry.
Do you see that, Doctor?
A I do.
Q Do you know if you were involved in that

poster presentation for this article?
A I was not at that meeting.
Q Okay. And the other article, the Findling article, that had been presented as a poster at some point; are you aware of that?
A I'm aware of that. I was not at the poster.
Q Okay. And is it not uncommon that not all the authors would necessarily be involved in presenting a poster for a particular article; is that fair to say?
A Inevitably one or at the most two would be there.
Q Okay. And I also want to note here on the same paragraph on the article, Doctor, that it notes that this manuscript was received at the American Journal of Psychiatry April 2, 2003. Revisions received September 16th and October 28th, 2003.
And the article was accepted October 31, 2003. Did I read that accurately?
A You did.
Q And Doctor, does that reflect to you that there was an exchange with the peer reviewers and with the journal regarding edits to this article and that ultimately, after that editorial process, the journal

accepted this article?
A So what would have happened is reviewed -- sent in April 2, reviewed and sent back to us. Changed. Went back on September 16th. Came back pretty quickly with a few minor changes and was accepted a month later.
Q Okay. And my point being that, Doctor, there's a give and take in the peer-review process between the authors and the reviewers and the journal that may lead to changes in an article; is that fair to say?
A Today most decent journals accept something below 33 percent, maybe 25 percent, maybe 15 percent of articles submitted. So most journals reject articles that are not of sufficient scientific standard.
And the ones that they do accept, they often ask for major decreases in length or major changes in the way it's written.
Q Okay. And as part of Mr. Gomez's deposition notice for the deposition today, he had asked you to look for any materials that may be related to the peer-review process for both the Findling article in 2003 and the what I'll call the Dunbar article from 2004.

Did you go back and look for those materials?
A I looked.
Q And other than what you had produced earlier today attached to the email that Mr. Gomez marked as Exhibit -- I believe it's 4 -- did you have any other materials relating to the peer-review process for these two articles?
A I had none. I moved office in 2006, and I culled everything that wasn't necessary in the move from one place to the next.
Q But ultimately, it's fair to say that, for both of these articles, they would have been reviewed by peer-reviewed clinicians or academics who would have made comments on the article. And there would have been some kind of editorial process before the articles were ultimately published in their journals; is that fair to say?
A They these are peer-reviewed publications, both of them.
Q Doctor, I don't think I have any more questions at this time. Thank you.
A Thank you.
MR. MOBLEY: I don't have any questions.
MR. GOMEZ: Doctor, I just have a few follow-ups.

EXAMINATION
BY MR. GOMEZ:
Q If you could put the RUP article back in front of you again. I think it's Exhibit 12. Mr. Essig showed you this article. It's a journal article, Society of Biological Psychiatry, in 2007; correct?
A Correct.
Q Okay. If you look on the first page, there's a sentence that begins, "Direct effects of elevated prolactin on breast tissue lead to galactorrhea in females and gynecomastia in males." Do you agree with that?
A Where are we looking?
Q Right over here, Doctor, about halfway down the right column. It begins, "Direct effects."
A Yes.
Q Okay. Again, the sentence reads, "Direct effects of elevated prolactin on breast tissue lead to galactorrhea in females and gynecomastia in males." Do you agree with that?
A No, I don't agree with that in that it's not a direct effect. It's an impact of it on the (INAUDIBLE) that leads to changes. So it's an indirect effect somehow.

Q Whether it's direct or indirect, would you agree with me that elevated prolactin can cause gynecomastia in males?
A You know, I'll say two things to that. I personally have never seen it as a condition, No. 1. And No. 2, at the levels that are present in the articles that we are talking about, I've certainly never seen it.
So I would have to -- having seen it in those levels in many different situations, I'd have to say that I have difficulty buying into that. And if you notice, that statement is not referenced. So it's a tough one to substantiate very easily.
Q Okay. It was written by George M. Anderson, Lawrence Scahill, and James T. McCracken, among others. Do you see those names?
A It's in the medical literature, but I'm unconvinced by it being a direct effect and at those lower levels. Let's leave it at that.
Q Okay. In the next paragraph, do you see where it says "however"?
A However?
Q "There's accumulating evidence that children treated with typical neuroleptics and risperidone often exhibit modest to marked elevations

in prolactin?
A Correct.
Q And the Findling article is cited, the 2003 article; correct?
A Yes.
Q Then it says, "Compared to adult patients, there is even greater uncertainty regarding the clinical implications of elevated prolactin in children and adolescents." Do you agree with that statement?
A Correct. So they didn't make an assumption from reading our article, the first one, that there was a definitive answer to the questions you've been asking today.
Q Okay. You would agree with me, by reading the Findling article in 2003, the authors of this article did not see the statistically significant association between elevated prolactin levels and side effects; agree?
MR. ESSIG: Objection to the form.
THE WITNESS: I'm not sure. They may have seen the raw numbers and seen that there wasn't a huge number of children with these problems.
BY MR. GOMEZ:
Q Sticking with this article, there's a

couple more things I want to ask you about. If you go to page 548, it's in the top left. Are you there?
A I'm there.
Q Okay. Up on the right-hand column, if you go down the --
A Okay.
Q There's a sentence beginning, "Findling et al. 2003"; do you see that?
A Yes.
Q Okay. It reads, "Findling et al. 2003 emphasized an apparent downward trend in serum prolactin when examined longitudinally from weeks four to seven through study end point at weeks 40 to 48." Did I read that correctly?
A Correctly.
MR. ESSIG: Chris, I'm lost.
MR. GOMEZ: I'm sorry. 548. Right there.
MR. ESSIG: Thank you.
BY MR. GOMEZ:
Q In this article, there's no mention of a statistically significant association at weeks eight to 12?
A Correct.
Q You were asked whether or not, looking at the final paper, you stand by the conclusions of the

article. I don't think you ever answered the question. Yes or no?
MR. ESSIG: Objection to the form.
THE WITNESS: The conclusions of --
BY MR. GOMEZ:
Q Let's get the final article.
A The conclusion of the article reads as follows: "With long-term risperidone treatment in children and adolescents, serum prolactin levels tend to rise and peak within the first one to two months and then steadily decline to values within or very close to the normal range by three to five months."
I stick by those conclusions.
Q You stick by the conclusion that you just read in the abstract; correct?
A Yes.
Q Okay. Can I have that for just a second? Do you stand by the statement, "There was no direct correlation between prolactin elevations and SHAP"?
A In the light of different approaches to statistical analysis, that has to be reevaluated.
Q Do you stand by the statement, "There was no direct correlation between prolactin elevation and SHAP"?
MR. ESSIG: Asked and answered.

BY MR. GOMEZ:
Q It asked for a yes or no answer. Do you have one?
A Given the later study which doesn't show any of those side effects, which confirm our findings, it appears that -- to say yes, that this is a defective sentence is correct. But does it nullify all the findings in that study?
I do not think so.
Q The study you're referring to is the 2007 article that you looked at?
A So what one does --
Q Yes or no answer, and then you can answer.
A Yes.
Q Okay.
A Okay. So the Findling article is in the literature. It's flawed by that sentence, yes. That's the answer to your question, yes. The subsequent literature looking at a not too dissimilar group of children comes up with very similar levels of prolactin and comes up with a very similar finding in terms of the side effects.
In fact, it finds none. So the medical literature is a series of building blocks. Sometimes the one block that's added topples the whole thing

over, and you have to start again. Sometimes it adds and creates a firm foundation.
This article -- and I couldn't find a whole lot of other articles that showed the reverse. This article adds to the Findling article in suggesting what happens to the prolactin levels in response to risperidone and the fact that there are not a lot of side effects.
Q One or two more questions. The Findling article of 2003 --
A Yes?
Q -- was designed to explore any relationship with side effects hypothetically attributable to prolactin and risperidone treatment; agree?
A Correct.
Q They found a statistically significant association at weeks eight to 12 in the all-inclusive SHAP A category; correct?
A Correct.
Q Yet this article failed to report that; do you agree?
A It reported it in an incorrect way.
Q Did the article --
A So "failed" suggests malice aforethought to me, and there was certainly none on the parts of

Findling, Moshang, and Daneman.
Q You interpret my use of the word "failed" as malice aforethought or intentional?
A Well, there's some suggestion of it in the discussion that's been going on today.
Q Assume for purposes of my question, when I say "fail," I mean that it was not in the article or the omission thereof. Okay?
A Yes.
Q Could have been done in a negligent manner, not with malice aforethought. This article failed to report the statistically significant association between elevated prolactin levels and SHAP; do you agree?
MR. ESSIG: Objection to the form. And foundation.
THE WITNESS: I think that's your assessment, yes.
BY MR. GOMEZ:
Q Do you agree with my assessment?
A To a degree, yes.
Q Fair enough. Thank you. That's all I have.
A Thank you.
MR. ESSIG: Doctor, thank you for your time

today.
VIDEOGRAPHER: This marks the end of videotape No. 3 and today's proceedings in the deposition of Dr. Denis Daneman. Going off the record at 1:19 p.m.
(Whereupon, at 1:19 p.m., the deposition was concluded.)

CERTIFICATE OF SHORTHAND REPORTER

I, Virlana Kardash, Registered Professional Reporter and Commissioner of Oaths in and for the Province of Ontario, before whom the foregoing proceedings were taken, do hereby certify that the witness whose testimony appears in the foregoing pages was duly sworn by me; that the testimony of said witness was taken by me stenographically at the time and place noted in the caption hereof and thereafter reduced to computer-aided transcription by me; that the foregoing transcript is a true and correct record of the proceedings; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in the outcome of the action.

_____

Virlana Kardash, RPR, CSR
Certified Shorthand Reporter
and Commissioner of Oaths

My certificate expires:
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