UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

BRIAN K. MILWARD, et al,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 07-11944-GAO
ACUITY SPECIALTY PRODUCTS GROUP, INC., et al,	)	
Defendants.	)	

BEFORE THE HONORABLE GEORGE A. O'TOOLE, JR.
UNITED STATES DISTRICT JUDGE

DAUBERT HEARING - DAY 4

John J. Moakley United States Courthouse
Courtroom No. 9
One Courthouse Way
Boston, Massachusetts 02210
Friday, April 24, 2009
9 a.m.

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I N D E X

P R O C E E D I N G S

THE CLERK: All rise.

Continuation of the Milward Daubert hearing. Be seated.

THE COURT: Good morning.

VOICES: Good morning.

MR. GRAY: Your Honor, if it would please the Court, the defendants would like to call Dr. David Pyatt.

DAVID PYATT, sworn

THE CLERK: State your name, spell your last name for the record, keep your voice up and speak into the mic so everyone can hear you in the courtroom.

THE WITNESS: All right. David Pyatt, P-Y-A-T-T, 1944 Cedar Ridge Circle, Superior, Colorado 80027.

MR. GRAY: Your Honor, if I could ask the Court to put on the PowerPoint screen?

THE COURT: You want the computer?

MR. GRAY: Yes.

And, your Honor, I apologize. I'm going to go back and forth between the PowerPoint and the ELMO a few times.

THE COURT: Fine.

DIRECT EXAMINATION

BY MR. GRAY:

Q. Good morning, Dr. Pyatt.

A. Good morning.

Q. Could you tell the Court --
A. Am I the right distance away from --
THE COURT: You're a little farther away. Pull the mic up to you. You have to be sort of on it.
THE WITNESS: How's that?
THE COURT: Better.
BY MR. GRAY:
Q. Have you prepared some slides to assist with your testimony today?
A. Yes.
Q. And this first slide has some background information. Would you tell the Court a little bit about yourself?
A. Okay. I have a Ph.D. in toxicology from of the University of Colorado. I was awarded that in 1995. I worked within the laboratory of Richard Irons, who is a world-renowned researcher on benzene, did some post-doctoral training there, got some grants, worked through the research faculty track, and eventually left and started my own company, which is Summit Toxicology, LLP, which I started in 2005.
I still maintain active academic appointments in several departments with the University of Colorado. I have an appointment at the School of Public Health where I teach a toxicology class; I have an appointment at the School of Pharmacy where I teach a risk assessment in environmental toxicology class; I teach a tox class in the Environmental

Health Sciences Program in the downtown Denver campus of the University of Colorado; and I teach physicians, graduate and medical students in those various courses.

Q. And I think your next line talks a little bit more detail about your background.

A. So, yeah, I've been doing this for about 20 years. I have a variety of abstracts and book chapters and peer-reviewed papers. Most of them have been either specifically on benzene or on bone marrow toxicity and immunological toxicity. Now, as a consultant, I work for a variety of agencies and private-sector clients, law firms, other consulting companies that come to me with, you know, specific requests. And I'm a member of a variety of scientific societies.

Q. And you prepared a report in this case; is that correct?

A. I did.

Q. Okay. And since you issued that report, have you continued to look at the reports issued by other experts and the depositions that were given in this case and continued to look at the literature?

A. Yes.

Q. Have any of the opinions that you've rendered that we've provided to the Court in your initial report -- have they changed materially since your report?

A. No.

Q. If we could go to the next slide, I would like you to tell

the Court in these next two slides what the primary things you're going to be talking about today are.

A. Well, I guess the big one is that there is, in my opinion, insufficient evidence to establish general causation between benzene exposure and acute promyelocytic leukemia, which is why we're here. The basis for that is it is a clearly distinct clinical entity, something we heard a lot about yesterday, and it's overly simplistic to just consider APL to be another subtype of AML; that the mechanistic sort of plausibility arguments are a little disjointed and don't really provide adequate evidence that a causal relationship exists.

The cell of origin, which we have been talking about in some detail, in my view it is pretty clear that the cell of origin for APL is different than the other subtypes of leukemia for sure, and most likely even different for the other subtypes of AML. And the one cytogenetic change, the translocation that we most strongly associate with APL, the 15;17, has never been shown in any assay, in vitro, in vivo; at no point has the 15;17 translocation ever been shown to be associated with benzene exposure.

And then the topoisomerase II argument, that's a pretty complicated argument and we will spend some time discussing that today, but collectively that is not sufficient evidence to link benzene with APL.

Q. Okay. So just to -- while you get some water -- to make

sure everyone has a roadmap, really the four things we're going to be talking about today are: distinct disease, cell of origin, topo II, and whether or not the evidence about chromosomal abnormalities establishes that benzene causes APL. Are those your primary four topics for today?

A. I think that sounds right.

Q. Okay. Let's go to the next slide. You've seen this slide before in, I believe, Dr. Bennett's and perhaps even Dr. Smith's testimony, correct?

A. Right. And the only reason why I'm bringing it up again is, you know, this is the hematopoietic hierarchy; this is the best representation of what we think is happening in the bone marrow where all of these mature cells that are listed along the bottom are arising from a pluripotential cell at the top. It isn't quite this linear, but it's the only way, really, that hematologists can depict what we think is occurring in the marrow.

What I like about this particular slide is it has a couple of really important breakpoints that will be important in what we're going to discuss today. And I think I can draw on this. So that area right there is important because once a cell has moved beyond that point, then -- that's pretty neat.

Okay. Once a cell has moved beyond that point, then it loses the ability to differentiate into one of those two main lineages. So the CMP, the common myeloid progenitor, or the

CLP, the common lymphoid progenitor, retains the ability to go down those lineages, the lymphoid or the myeloid, but it has lost the ability to go down the other ones. So that is a pretty distinct differentiation point in this hierarchy.

Q. Can I interrupt you for one second, Dr. Pyatt? Just so the record is clear when someone's reading this without the benefit of the slides, that breakpoint is the point at which a cell either goes down the lymphoid line to the CMP or down the CLP line. Is that the breakpoint we're talking about there?

A. Well, yeah. I'm talking about this break right here where I've indicated where this purple cell above, that one, which doesn't really have a name, but that cell theoretically retains the ability to turn itself into any kind of lymphocyte or any kind of myeloid cell. And then once it differentiates, it becomes what is called lineage committed, and it has now committed to becoming either a myeloid cell or a lymphoid cell.

So the next step is it becomes a common precursor, or a common progenitor, common myeloid or common lymphoid, and those retain the ability to differentiate into others, but they have lost the ability to cross over. So a common myeloid cell will not give rise to a T lymphocyte, for example, and a common lymphoid precursor will not give rise to a granulocyte or other myeloid cells. Does that make it clearer?

Q. Yes, that does.

A. Okay. The other thing to point out on this slide are the

boxes over on the left. There's a lot of complicated nomenclature in there, but that demonstrates, or describes, the phenotype of these various cells. And as you heard yesterday, the phenotypic description of the phenotype are the proteins that are expressed on the surface that allow hematologists to identify these cells and allow hematologists to really separate out various cell populations using flow cytometry.

And the ones that I think are important, if you look at the white box to the left of the hematopoietic stem cell at the very top, you'll see that that is CD34+ -- so that is an important marker that indicates a stem or progenitor cell -- and it is CD38-. That is also a very important marker. When you go down the list, and now you're past -- when you move down to about this level we were discussing, you see that the CD38 becomes positive. So when you see a "CD38+" expression on the surface of the cell, that gives you some indication as to where in the maturation flowchart that particular cell is likely to arise. So that is an important distinction that you can get from looking at this slide.

Q. Okay. We've heard a lot of testimony about it, but I want to make sure we're very clear today. Can you talk a little bit about what a -- what the hematopoietic stem cell is and then differentiate that from what we've been describing as a leukemic stem cell?

A. Yeah. And just as Dr. Bennett pointed out yesterday, the

nomenclature is somewhat confusing because they both have the word "stem cell" in there. But a hematopoietic stem cell, or a pluripotential stem cell, is a hematopoietic cell -- which is up here at the top -- that theoretically has the ability to turn itself into all of the different lineages -- all the different blood lineages.

A leukemic stem cell, even though it still has the word "stem" in it, is just a cell that can give rise to that form of leukemia. So a leukemic stem cell can be anywhere within this hierarchy; it has the ability to self-renew and to give rise to that particular form of leukemia. It does not mean that it always arises at the hematopoietic stem cell level, and in a lot of cases I think it does not.

Q. And do researchers now believe that some cells that previously didn't have the ability to self-renew through the carcinogenic process gain that ability and become leukemic stem cells?

A. That was one of the really interesting and important findings in the Wojiski paper that we discussed in some detail yesterday. Researchers demonstrated that really mature granulocytes, all the way down here in this area, when they had the 15;17 put into them, they achieved the ability for self-renewal, so they became the leukemic stem cell for that disease even though they are very differentiated.

Q. Now, even before the Wojiski paper, this concept of a

leukemic stem cell was established in the literature, correct?
A. Well, the leukemic stem cell concept has been around for about ten years, and it's been evolving and people are thinking about it in different ways. And it really has to do with therapy. I mean, that really is where the most -- that's where it's the most useful. Because the idea is if you're treating a leukemia with whatever your therapy is, but you're not treating the leukemic stem cell because it's quiescent or it's hidden or whatever the reasons are, then you're going to relapse, all right?

So people like John Bennett and others in the field, treating oncologists, are keenly interested in the leukemic stem cell so that they can derive therapies to try to kill those cells as well so that they can effect some kind of long-term remission or actually cure a patient.
Q. Earlier when you talked about the findings in the Wojiski paper that suggest that the leukemic stem cell for APL is where you marked, the point you marked on this slide, the hematopoietic hierarchy, was below the GMP cell; is that fair?
A. Yeah. I mean, you can't take any of those quite literally because in this particular hierarchy there's only two cells drawn between a GMP and a granulocyte. There are other more complicated flowcharts where there might be as many as four steps of differentiation between those. But, yes, I think that area right in there is where that paper indicates that it

happened.

Q. And of course we --

THE COURT: Excuse me. Can I just ask him about the chart? Is this a chart that was prepared for this presentation or does this come from a piece of literature?

THE WITNESS: It comes from the literature.

BY MR. GRAY:

Q. And, Dr. Pyatt, just so we're clear before we move on, APL manifests in -- within this granulocytic line of cells that we see on this chart, correct?

A. I'm sorry. Could you ask that again?

Q. APL appears within this granulocytic line of cells; is that correct?

A. Yes. Yes. APL, acute promyelocytic leukemia, is a leukemia that is that cell.

Q. The cell just below the GMP but before the granulocytes, it's in that range?

A. Correct. It's a promyelocyte. In this lineage diagram there's only one cell, so I'm calling that the promyelocyte. In other lineages there could be meta promyelocytes and others there. And then you would have to point out the promyelo- -- it's going to be in that region.

Q. This is a much simpler slide of what could be used in a graduate course on cell biology; is that fair?

A. Yeah. I mean, you could get them in a variety of

different degrees of complication. And really it depends on what you're interested in. If what you're trying to determine or discuss are the lymphoid differentiation markers, then they may ignore the myeloid markers completely and elaborate more on the lymphocyte. So you'll see them all different ways.

Q. Okay. Fair enough.

If we could go to the next slide.

So, now, again, on the four points we're going to talk about today, Dr. Bennett touched on this yesterday, but could you briefly give the Court your opinion, and a brief description for the basis for it, about whether or not APL is a distinct disease from other subtypes of AML?

A. I think that's pretty clear both from what he said as well as what's on this slide. I mean, the prognosis of APL is very different than most other subtypes of AML. The treatment is unique in the hematology/oncology community. All of the other chemotherapeutic agents that are used to treat AML are cytotoxic, you know, that kill the dividing cells. That's how it works.

With APL, it's the only disease where the treatment, all-trans retinoic acid, doesn't kill the cells; what it does is cause the cells to take that next step in the differentiation pathway. When they take that next step and they differentiate into a granulocyte, then they die on their own. Granulocytes have a relatively short half-life; they only

live for six or eight hours. So they take that next step and then they die. There's no other leukemia that I'm aware of that that methodology is used to treat it. And it's very successful.

So yesterday -- Dr. Bennett talked yesterday in some detail about the cytogenetics and what the disease looks like morphologically. We will spend some time today discussing the cell origin and the last two points, but I do think that the ideology is different and that there is evidence that the epidemiology is different for this particular subtype.

Q. Okay. If we could go to the next slide.

Now, do you believe it's appropriate to assume that if one agent causes one form of AML, it therefore causes all forms of AML?

A. I don't think that would be appropriate to assume now. It might have been appropriate to assume 25 years ago, but I think there has been evidence that is indicating that that is too simplistic a view, and that you need to evaluate -- when you can, you need to evaluate the various subtypes. And keep in mind that even the subtypes are a relatively broad category. I think where the field is going, it's going to be looking at specific cytogenetic markers and what is the epidemiology associated with an 8;21 translocation or an inverse 116. In this case the 15;17 and the APL are essentially the same thing, so we've already taken that step.

Q. And do you believe that looking at the relationship between cigarette smoke and APL is a good illustration of the point you just made about one agent doesn't cause all forms necessarily?

A. I do. I mean, it's been well established from a lot of different researchers, and the surgeon general has now accepted it and everyone pretty much is on the same page, that AML is -- that cigarette smoking is an established risk factor for AML. So if you simply said that all of the subtypes of AML are going to be equally affected by cigarette smoking, I think in this case you would be wrong; that would be too simplistic of a view. So this is a good illustration really of where APL is a distinct epidemiological entity from the other subtypes of AML.

Q. Okay. So there's actually studies where the incidence of APL among smokers has been separately analyzed. And you're going to tell us about some of those studies, right?

A. I am. There are three that I found where they have done this, and in all three cases -- we'll go through them. So this first one by Moorman was published in the British Journal in 2002. And what they were interested in was the cytogenetics. But, again, since APL and 15;17 are almost synonymous, that's essentially what they're looking at.

And if you look right here at the current smokers, first of all, you see a small -- 1.42, which is about right -- but a statistically significant increase with current smoking and

AML. But with APL, 15;17, the risk is .47, which is a decrease. And in this case it is statistically significantly decreased. So just based on that one finding, if you just say smoking causes AML and didn't say anything else about it, really that would be incorrect; it doesn't cause all forms of AML based on this study.

Q. Okay. And if we go to the next slide -- there's more than one study, correct?

A. Yes. So this one was published in the Journal of the National Cancer Institute. I don't know any of these researchers, but I'm assuming some of them are there. That's usually how it works.

Q. Is it the Sandler paper?

A. The Sandler paper, yes, from 1993.

But it shows the same thing. If you look at the M3 category -- well, right there, the total odds ratio is .56, confidence interval of .30 to 1.03, so that is suppressed but not statistically significant because the other 95 percent confidence interval is greater than 1.0. With the less-than-60-year-olds the relative risk is .42, and with that particular group it is statistically significant. The over-60 group, the relative risk is elevated -- the odds ratio is elevated at 3.05 -- but they have really wide confidence intervals, .26 to 36.0, and that's because there was one case. There was one case that was in that category. So that's why

you see such wide confidence intervals.

But, again, it supports the position that APL is not elevated associated with cigarette smoking.

Q. And, again, when you pool the under-60 and the over-60 group, the odds ratio for M3 for everyone in the study was .56, correct?

A. Right. .56 with a clearly suppressed -- but it was not statistically significantly suppressed -- odds ratio.

Q. This study is further evidence that smoking does not cause APL. You'd agree?

A. That's correct.

Q. Now, let's look at -- Sandler actually commented on these findings, and I'll read these for the record. This is from the Sandler paper at page -- I believe it's 1999. "There was a nearly significant inverse association between smoking and t(15;17)(q22;q12) with an odds ratio of 0.42 (95 percent confidence interval 1.17 - 1.01) when patients with this abnormality were compared to control subjects. All of the patients with this abnormality had leukemia classified with M3, which was also inversely associated with smoking."

So the authors here believe that the data in the paper -- presented in the paper -- show no increased rate associated with smoking; is that a fair statement?

A. Sure. I mean, I don't know what else they could conclude from looking at that data.

Q. Okay. Now let's look at the Björk paper.

A. So this one was published in Leukemia Research in 2001. And, again, they went in and looked at the various subtypes of AML that were associated with cigarette smoking. And you can see, like, the M6, for example, down here is very high, 8.9, an odds ratio. But consistent with the other literature that we've been looking at, the AML-M3 --

This doesn't really show up right where you touch it, but... Okay. Everyone can see that.

-- the odds ratio is .32, which clearly is suppressed in this case.

Again, it doesn't quite achieve statistically significant suppression; you have a confidence interval of 1.0, but it is going in that direction, and it is totally consistent with the other studies.

Now, I'm not aware of any studies that have done this, that have found contrary findings that have shown that APL is, in fact, increased in smoking populations. There are several studies out there that say it's pretty complicated and it's fuzzy and it's hard to get a clear picture. To the extent that I'm aware where they have broken out the subtypes, they all seem to say the same thing, and that is that APL does not appear to be associated with cigarette smoking.

Q. So based on this research and the smoking and APL, Dr. Pyatt, it's apparent that it causes some forms of leukemia but

does not cause others; fair?
A. That is certainly the take-home message from this. If you were to assume that smoking causes AML -- all forms of AML -- that would be an overly simplistic view based on this data.
Q. Is benzene found in cigarettes?
A. It is. Benzene's found in cigarette smoke as well as benzene metabolites.
Q. And Dr. Smith has testified that he believes it's the benzene in cigarette smoke that contributes to the increased risk of AML among smokers. Are you familiar with that opinion of Dr. Smith's?
A. I heard him say it on Tuesday, and I've heard him say it before, yes.
Q. Do you agree with that opinion?
A. I don't. I don't. I don't agree with that because I don't think there's enough benzene in cigarette smoke to achieve, you know, a quantitative increase in risk, but I know that's what he thinks.
Q. And how does that affect Dr. Smith's overall opinion that benzene must -- he's got an opinion that benzene causes APL, and he also has an opinion that the benzene in cigarette smoke is what leads to AML. Are those two positions inconsistent?
A. They're completely inconsistent.
Q. And that's because if benzene is driving the increased risk of AML in cigarette smoke, it's not driving any increased

risk from smoking in APL, fair?
A. That's true.
Q. Okay. Now --
A. The only reason why I brought it up, really, was not so much that it has to do with benzene, although that is an important point, but that it illustrates that you cannot just assume that all the different subtypes of AML collectively are going to share the same set of risk factors. That was the point that I had for bringing up this literature.
Q. And if we could go to the next slide.
Have other researchers also commented on this -- on the relationship between smoking and APL?
A. Yes. The "Epidemiology of APL" paper by Dr. Douer in 2003 that was also discussed in some detail in this proceeding states that "AML was found to be associated with smoking - in particular, the FAB M2 subtypes or changes in Chromosome 8. Interestingly, this association was not found with APL."
Q. Okay. Let's go to the next slide.
And I don't want to get too far down the road of the epidemiology -- we've heard a lot about it -- but as you read Dr. Douer's paper, what were his opinions about whether or not there was a separate set of epidemiological principles at play for APL as opposed to some other subtype?
A. I think there have been a lot of investigators who have been curious as to whether subtypes of AML are all equally

affected by risk factors for AML, and we've talked a lot about those, and they've been up on the board, different slides this week.

But Dr. Douer wrote an epidemiology paper, view paper, specifically on this topic, and tried to pull together the literature that he found related to the acute promyelocytic leukemia subtype, and took the position, which I think is accurate, that it is a very unique subtype, which is what he says. "APL is an example of a truly unique AML subtype that has an easy-to-recognize morphology associated uniformly with the distinct chromosomal and gene rearrangements. Thus, APL is amenable to epidemiology studies." And then later in the abstract, "It is therefore likely that etiological factors for APL are different from those of other AML subtypes. So far no environmental and/or occupational risk factors have been found for APL."

Q. Okay. Yesterday in the context of discussion of this paper, and perhaps the day before, we heard a lot of talk about the Mele paper, the shoemaker study; do you recall that?

A. Yes.

Q. And to briefly go into that, there was some discussion about how the -- there was suggestion that maybe Dr. Douer didn't appropriately consider the Mele paper when reaching these conclusions. Do you recall some of that cross-examination?

A. I heard a little bit of it, yes.
Q. Have you reviewed Dr. Smith's deposition testimony about his opinions about the Mele paper?
A. Yes.
MR. GRAY: Your Honor, if I could switch the ELMO briefly.
BY MR. GRAY:
Q. And I'm at page 50 where I believe Mr. Leghorn was asking Dr. Smith about the significance of the Mele paper. And he's asked, "Doctor, the finding of only two cases, does that affect the study?" Dr. Smith replies on page 51, "Yes; it's not particularly strong. I mean, even though they say there's a strong association with the shoemaking, it is actually based on few cases."
"Mr. Leghorn: And your comment was that that's not a particularly strong finding; is that right?"
"Answer: Well, it's strong in terms of the odds ratio, but in terms of a definitive finding, one would want to have more information."
That was the testimony of Dr. Smith; would you agree?
A. That's my understanding, yes.
Q. And do you agree with Dr. Smith, setting aside the question of were those few workers exposed to benzene or not -- the Mele paper is a -- not a very strong finding based on two reported cases of APL?

A. Yeah. No matter what you say about the exposures and whether they had them or not, there were still only two cases of APL in the shoe workers' group, which is a very small -- very small study. And when the studies are that small and you've only got one or two cases, misclassification and other things that can happen are hugely important.

MR. GRAY: If we could go back to the PowerPoint view, your Honor.

BY MR. GRAY:

Q. And, again, Dr. Douer had the Mele paper available to him when he reached the conclusions that he reached in this paper, correct?

A. That's my understanding. And he felt the same way that I think most people that read that would feel, and that is that it is not a very strong finding.

Q. Okay. Let's go to the next slide. Actually, we need to go backwards. Back one more briefly. Okay. Now forward. Thank you.

Okay. So we've talked about APL as a distinct disease with separate etiological risk factors. And now let's move on to the rest of your testimony. And this slide lays out three hypotheses that Dr. Smith has regarding biological plausibility. Can you very quickly give the Court just the bullet points before we move on to the first topic?

A. Yeah. I think what we're going to end up discussing

relative to Dr. Smith's testimony is the cell-of-origin discussion and whether or not the evidence supports that ALMs, or all leukemias, come from the same stem cell; the 15;17 translocation again, this notion that simply because benzene has been shown to cause some balance translocations, therefore, it's biologically plausible that it can cause the 15;17 translocation; and then this whole discussion on topoisomerase II, which is pretty fundamental to Dr. Smith's biological plausibility position.

Q. Okay. So three hypotheses: Number one, there's a common cell of origin for AMLs; number two, since benzene causes some balanced translocations, it therefore causes the t(15;17); number three, benzene causes leukemia via topo II inhibition.

Do you believe, Doctor, any of those three hypotheses have been established in the scientific community?

A. No.

Q. Let's go, then, to the first topic, cell of origin. I'll read here. This is from Paragraph 28 of Dr. Smith's report, and I'll read a sentence here, Paragraph 28A. Actually, I'll start with 28. "It is biologically plausible that benzene causes APL for a number of reasons.

"First" -- and this is the cell-of-origin argument. "First, the subtypes of AML are, in fact, subtypes of one disease inasmuch as they all derive from a genetically damaged pluripotent stem cell which can differentiate into all

myelogenous stem cells and proliferate."

I didn't read the whole paragraph, but is that your understanding of the position that Dr. Smith has taken, at least in some point in this case?

A. He clearly took it when he wrote this. And he sort of had that position during his deposition, if I recall. But then his testimony on Tuesday seemed like he was backing away from this a little and that he was acknowledging that there were -- he was using more plural terminology. And instead of saying "They're all coming from a single stem cell" he was saying "stem" or "progenitor cells," which opens up the possibility that they're different. So I don't honestly know where he stands today.

Q. Okay. Well, let's talk about your opinions from here, then. Let's go to the next slide.

If all leukemia -- if all AMLs derived from a pluripotent stem cell, what would be the cell of origin, as you understand that phrase, on this chart entitled "Hematopoietic Hierarchy," which is a repeat of the slide we showed earlier?

A. Well, historically, the way experimental hematologists have used this vernacular -- have used these terminologies -- is that a pluripotential stem cell is this. It's at the top.

Q. The HSC?

A. The HSC. That stands for "hematopoietic stem cell," which is pluripotent in that it can differentiate into everything.

Once it leaves that state and starts differentiating, maturing, then it is no longer called a stem cell and it becomes a precursor or a progenitor cell. And that is historically the way these things have been divided out. So when you say "stem" or "progenitor cell," well, that opens up a lot. When you say a "hematopoietic" or a "pluripotential stem cell," that is this cell at the very top.

Q. Okay. And progenitor cells, as evidenced on this slide, are really throughout the hematopoietic hierarchy until you get to a mature effecter cell; is that correct?

A. Correct. You have multipotent and, you know, the oligopotent -- and that's neither here nor there. But you've got a lot of differentiation capacity. And as they move down this hierarchy they become more and more lineage-committed, which means they lose the ability to turn into other things. But all that time they are still considered progenitor cells.

Q. And certainly some scientists believe that the cell of origin for some types of AML, including APL, is a lineage-committed progenitor cell; is that right?

A. We heard a lot about that yesterday from Dr. Bennett, and from many of the studies, so, yes.

Q. And what is your opinion about the cell of origin for APL?

A. Well, I think collectively the literature that I looked at prior, that I cited in my original report, that I looked at after Dr. Smith criticized that conclusion, all of that

literature collectively still pretty much reinforces to me that it's somewhere in this area down here; that that is where APL is most likely to arise.

Q. And the area you marked is well below the CMP cell, correct?

A. That seems to be the case, yes, that it is below the common myeloid progenitor. And there's some data that we have not talked about yet that would support why that is true.

Q. Okay. And the significance of that is if the APL originates at the CMP cell or above, then that gives some credence to the theory that Dr. Smith is right that it's biologically plausible that benzene causes APL; is that fair?

A. Well, I mean, I guess even if it's down here it doesn't completely rule out that benzene can cause APL. I mean, all it's saying is that they are not all coming from the same cell. So that's really what I took issue with, and that's what we've been discussing, that the evidence is pretty clear, in my view, that the forms of leukemia in general and the subtypes of AML specifically do not necessarily arise from the same stem cell -- or the same cell, irregardless of where it is.

Q. And I want to make sure it's clear: You can't point to -- and Dr. Smith can't point to -- the exact cell with certainty that is the cell of origin for cancer with 100 percent certainty, can you?

A. For APL --

Q. For APL.
A. -- or for cancer in general?
Q. For any type of -- for APL. Can you point with certainty and say, "That's the one. I know it 100 percent"?
A. No. No one can do that.
Q. Your point is that the weight of the evidence is that it's at a committed cell as opposed to a cell higher in the hierarchy?
A. That position is absolutely consistent with all of the scientific data that exists on this topic. Every one of the authors that are presenting some little piece of this puzzle will say, "But you can't rule it out and it's still a possibility" because no one knows with absolute certainty. But when you look at all of the pieces of the puzzle together, each one rules out that it is likely occurring in these different places, and you're left with somewhere down the granulocytic pathway that the cell has been committed not only to a myeloid path but to a granulocytic path.
Q. Okay. And if we could go to the next slide --
THE COURT: Could I just ask: As a point of reference can you determine that the cell has become leukemic after the 15;17 translocation but not before? Can you make that determination?
THE WITNESS: I think that's true. I mean, since we --

THE COURT: So the question becomes not -- let me ask it more specifically, I guess. You could ask when, at what stage of maturation, does the translocation occur?

THE WITNESS: That is exactly right, your Honor. And that is exactly what the various authors in these studies have done. They have gone to these various lineages and said, "At what point do we see the 15;17 translocation and at what point do we not see that?" And so, then, that is really the basis for them saying that "We think it's happening at this level of maturation or within these lineages." That's exactly right.

MR. GRAY: And actually, if I could ask Mr. Weathers, will you skip ahead to the Chang slide? Just to further answer that question, your Honor, Dr. Pyatt has a study that he brought that is relative to that that maybe we could go straight to.

THE WITNESS: Sure. In the Chang 2005 "Cancer Genetics and Cytogenics" -- anyway, what they did in this study was try to determine -- they looked at patients that had APL. And they isolated various populations from those patients, the hematopoietic populations, and said, "Where do we see the 15;17?" And taken at the abstract, they did not see the 15;17 in T-cells, they did not see the 15;17 in B-cells, and they did not see the 15;17 in erythroblasts.

So if you go back to -- so I drew the little red boxes on there to illustrate just what that one piece of data would

do kind of to your cell-of-origin argument. And so that they didn't see it in a T-cell --

BY MR. GRAY:

Q. And just for the record, you're looking at the Hematopoietic Hierarchy slide that follows the Chang slide?

A. Sure. Yes. And they didn't see it in B-cells, no one looked in the NK-cells and no one looked in dendritic cells, but I think most people would agree that that means that it probably has not occurred -- I mean, it has occurred after that differentiation step because the 15;17 is not being found in any of the lymphoid cells. So that puts it probably somewhere around the common myeloid progenitor cell.

And over on the other side, the erythrocytes, they didn't find it in the precursors to the red blood cells, so that knocks out another one of those little branches. So every time they do that, that's one of the pieces of the puzzle that I was discussing. It is narrowing down where it is likely that that 15;17 actually arises.

Q. And so this study is further support for your opinion that the 15;17, and therefore APL, arises at a committed granulocytic progenitor, correct?

A. That would certainly be consistent with this data; yes.

MR. GRAY: I would ask if we could go backwards two or three slides.

BY MR. GRAY:

Q. Now, when you issued your report where you addressed this cell-of-origin issue, you quoted a textbook by Dr. Jandl. Can you tell us a little bit about Dr. Jandl -- I believe he's deceased now -- and this textbook?

A. I don't know about him personally, but he wrote what, at least in my training, was the definitive textbook on hematopoiesis and blood disorders. And it was called Blood. And I used it all through my training, and so I used it to support my opinion because this is what he says: "The cell of origin for AML is the pluripotential stem cell, CFU-GEMM" -- which is one step downstream from the pluripotential stem cell -- "in some cases and progenitor cells lower (more mature) in the hierarchy in others."

And he was specifically talking about APL in that latter part, "more mature."

MR. GRAY: Okay. Let's go to the next slide.

BY MR. GRAY:

Q. Dr. Smith had some pretty harsh criticisms for this opinion; is that fair?

A. I paid attention to him.

Q. Okay. Well, I'll read what he said in his supplemental report. "For this criticism that my assertion is false, Dr. Pyatt cites a textbook from 1997 by Jandl that, like Dr. Pyatt's position, is completely out of date. Jandl's textbook was written before the discovery of leukemic stem cells a

decade ago which has completely changed our understanding of the pathogenesis of leukemia.

"All active researchers that I know in this field understand this concept and do not debate whether benzene causes only some forms of AML but not others."

Do you recall reading that in Dr. Smith's report?

A. I do.

Q. What did you do after you read that in his report?

A. Well, like I said, I took that very seriously. I mean, the citation that I put in my report from Jandl (1997) really just verified everything that I had been taught, everything that I had learned up to that point, what I thought the literature had been saying. And I wasn't just sitting in my office for the last ten years doing nothing; I've been reading papers on leukemia pathogenesis throughout my career. I watched the development of the leukemic stem cells. I understood their significance and what people were thinking about them. But I wanted to make sure that -- and I had never seen this concept of leukemic stem cell radically change our understanding of the potential cell of origin. But I took Dr. Smith at his word that my textbook was out of date and, therefore, my opinion was out of date. So I went to the literature to see if that was true.

Q. Okay. And let's talk about some of those papers that you found. Let's go to the next slide.

A. One of them we just talked about, the Chang paper.
Q. The paper by Chang found that 15;17 was not detectable in several other blood lines, correct?
A. That's correct. Which is absolutely consistent with what Dr. Jandl put in his overview of the cell of origin for leukemias.
Q. And that's absolutely consistent with your opinion you've given about the cell of origin for APL?
A. It is.
Q. And let's go to the next slide.

Okay. This is the slide that we've already discussed about Chang. So let's go to the next one.

Dr. Bennett described the study by Turhan in '95. But if you would, let's reintroduce the Court to that paper.
A. So this one was similar in that they looked at APL patients and, again, using the phenotypic markers which I discussed earlier, tried to establish where in the hierarchy of hematopoietic differentiation do you find the 15;17 -- do you find that translocation.

And what they say is that the CD34+/CD38- antigen, meaning those very primitive cells at the top of the flowchart that are CD38-, those are not involved in the neoplastic process of APL. So this -- another piece of the puzzle puts it at the bottom half of that hierarchy where the cells are CD38+. And I think we have a slide of that.

Q. Can I back up, though, just briefly, to that study?
A. Sure.
Q. And to identify the cells they wanted to stain with these markers, they actually performed this analysis on the cells that had the t(15;17), correct?
A. That's right.
Q. So, again, they looked at the t(15;17) cells. They put the markers on them. The markers tell us are these cells that are high up in the hierarchy or are they low at the --
A. Right. I think they tried to do it the other way around. I think they probably used the CD38 as a method to separate out these populations using flow cytometry, and then looked to see whether the 15;17 was present in those two populations. And they found it in the CD38+, but they did not find it in the CD38-.
Q. So this paper is very consistent with Chang's results ten years later? Let me ask that a different way. This paper supports what Jandl said in '97, correct?
A. Absolutely.
Q. And it supports what you said in your report, does it not?
A. It does.
Q. Okay. Let's go to the next slide. This is the Wojiski paper that we've heard a little bit about already. But please tell the Court the significance of the findings in this paper.
A. This was a different type of study. And like Dr. Bennett

discussed yesterday, it's pretty complicated, what they did. But essentially what they attempted to do was to understand at what level of differentiation can the 15;17 cause self-renewal. Can you make, basically, a leukemic stem cell at these really differentiated cells if you put into them the 15;17 translocation. And the methods for doing that are pretty complicated, but it doesn't matter.

Essentially, what they said was, "These findings are consistent with the hypothesis that cancer stem cells may arise from committed progenitors that lack stem cell properties."

So what Dr. Bennett pointed out yesterday was that they were relatively mature cells, heading down the granulocytic pathway consistent with his clinical observations that they're HLA-DR positive and these other things that he talked about that put it down that committed -- myeloid committed path.

Q. Okay. Let's go to the next slide.

So when we talk about a committed granulocytic pathway, we're talking roughly the area that we've got marked in blue here? Is that --

A. That is consistent with all of the existing data; yes.

Q. Okay. So the Wojiski paper from 2009 -- which actually came out after your deposition, right?

A. The Wojiski paper? Yes.

Q. Okay.

-- that supports the statements by Jandl in '97?

A. Completely.
Q. And supports your opinions in this case?
A. Yes.
Q. Having gone back and reviewed this literature, do you agree with Dr. Smith that the opinion in your report was completely out of date?
A. That is not true.
Q. Okay. And in his supplemental report, Dr. Smith actually quoted from the abstract from a few papers that I'd like to talk about as well. Do you recall the papers that he quoted in his supplemental report?
A. In support of his position that they can all come from the same cell, yes, I do.
MR. GRAY: Your Honor, if we could switch to the ELMO.
THE COURT: Let me ask an informational question quickly. What does the acronym "GMP" stand for on that chart?
THE WITNESS: "GMP" stands for "granulocyte macrophage" -- or "monocyte precursor." So you could see that one still has the ability to turn into granulocytes or macrophages.
BY MR. GRAY:
Q. Okay. And is that how --
THE COURT: I'll give it back to you. Go ahead.
BY MR. GRAY:
Q. I was going to ask you to point out, for example, that's

how other designations on the chart are made. For example, "MEP" relates to the ability to form an erythrocyte or a platelet, correct?

A. Megakaryocytic. The "M" stands for "megakaryocytic," which is the big cell that produces platelets, and the "E" stands for "erythroblasts," and then "P," yeah, the precursor or progenitor.

Q. And the "P," is that for "platelet"?

A. No. "P" is for "progenitor." So "MEP" would be "megakaryocytic erythroblasts" or "erythrocytic progenitor."

Q. Okay. Let's go back to the ELMO.

So this is the Misaghian paper from 2008 that Dr. Smith cited for support that he is right that there's one common cell of origin for all AMLs and that you're wrong. I've got a quote I've highlighted here. I'm just going to read it, Dr. Pyatt. "Some studies suggest that the original target of cellular transformation of the LSC arises from the HSC compartment. However, other studies by Cozzio, et al, using lethally irradiated recipient mice, have demonstrated that the oncogenic...chromosomal translocations can transform not only HSCs, but also myeloid-restricted progenitors that lack self-renewal capacity."

Did I read that correctly?

A. Yeah, except for the dot, dot, dots. But yes, you did.

(Laughter.)

BY MR. GRAY:

Q. I wanted to make sure you were listening very carefully.

Does that statement in the Misaghian paper support what you've been saying all along?

A. It does.

Q. I've got one more paper to put up on the ELMO that Dr. Smith cited as proof that you were out of date. And this is the Passegué paper from 2003. And I'll read from this. "Although HSCs are often the target of genetic events leading to malignant transformations, committed progenitors or even differentiated cells may also become transformed. In APML patient samples, the M3 subtype of AML, it has been shown that the APML associated fusion gene PML/retinoic acid receptor RAR-alpha, which can result from the t(15;17) balanced reciprocal translocation, was present in the CD34-/CD38+ cell populations but not in CD34+/CD38- HSC enriched-cell populations. This observation suggests that in APML the transformation process may involve a more differentiated cell type than HSCs and/or pluripotent progenitors that have been implicated in other AML subtypes."

I think I did a little bit better job reading that one.

Does -- when Passegué is talking about APML, they're talking about AML, correct?

A. Yeah, it's just a different acronym. Acute promyelocytic leukemia is what APML stands for.

Q. And this reference to the CD34-/CD38+ study that goes to Footnote 76, they're actually referring there to the Turhan paper from 1995 that we've already discussed, correct?
A. Correct.
Q. So the evidence about the cell of origin in APL that existed before '97 that Jandl was relying upon is still cited in recent literature as very relevant, correct?
A. Yes, it is.
Q. And does the passage I read from Passegué further support your opinion about the cell of origin of APL that we've been discussing?
A. I certainly think it does, yes.
Q. Now, I want to show on the ELMO a slide from Dr. Smith's presentation. And I believe the second bullet point there is related to the cell-of-origin argument. I'm not exactly sure. But the slide said, "Benzene is an established cause of AML and acts in at least two ways to cause leukemia. The second way is it recruits stem cells into dividing." And there Dr. Smith cited a paper by Richard Irons from 1992?
A. Yes.
Q. Do you recall that testimony?
A. I recall that paper.
Q. Okay. You were actually working with Dr. Irons' group when that research was being finished up for that paper; is that right?

A. I was. I had just joined the Irons lab three or four months prior to the publication of that paper.
Q. Okay. And we're not going to go into detail about the paper, but I've got it up on the ELMO. The paper is "Synergistic Action of the Benzene Metabolite Hydroquinone on Myelopoietic Stimulating Activity of Granulocyte/Macrophage Colony Stimulating Factor In Vitro"?
A. It's a mouthful, I understand.
Q. You weren't listed as an author on that paper, because that paper was well underway when you arrived to the Irons group?
A. Yes. Yes, I wasn't.
Q. Let me ask you about this paper. Did this paper conclude that benzene causes APL through stem cell recruitment?
A. No.
Q. Okay. What did Irons and his group find in this paper? It was a mouse study, correct?
A. It was.
Q. What did they find in these mice?
A. We were using C56 -- it doesn't matter what kind of mice we were using, but basically we were taking the bone marrow cells out of the mice, treating them with benzene metabolites, and then observing their responsiveness to various growth factors. One of the things that we never discussed in these hierarchies, because it's just one more layer of complexity, is

that what drives that differentiation is their responsiveness to growth factors. And so early cells don't have receptors for the growth factors, so they ignore it. When they take another step toward maturation, they express a receptor for that growth factor and then they respond to it. So that is what orchestrates this whole process.

So what we were looking at was how can benzene, if at all, or its metabolites, change the way these cells respond to the various growth factors. And the ones that they were using, which we used throughout, was GM, granulocytic macrophage, colony stimulating factor so the colony is -- well, we'll get to that. But that's how you assay these cells.

Q. Okay. And what you found -- or what the Irons group found was that the benzene metabolites accelerated the growth of the cells from that colony; is that right?

A. That -- not quite. What we found, and what was reported in this paper, was that cells treated with hydroquinone became more responsive to the growth factor. They didn't grow any faster, but more of them responded to the growth factor. So the idea is that perhaps what hydroquinone is doing is pulling more primitive cells into a place where they can respond to that growth factor that we could then measure -- or was measured in this colony-forming unit assay. That was the essence of this paper.

Q. Okay. Are you aware of the Irons group ever replicating

these findings in mice in humans or human cells?

A. To my knowledge it's never been published, for sure.

Q. Okay. Now, on cross-examination of Dr. Smith, Mr. Leghorn pointed out to Dr. Smith that the paper that has Lan as the first author, but Dr. Smith wanted us all to know that he actually wrote, that the findings of Lan in human populations were inconsistent with the findings in the Irons paper.

Can you explain whether there's an inconsistency -- and if so, why -- between the Irons findings of -- well, if you can explain the inconsistencies.

A. Yeah, well, it's totally opposite. If you look at the second panel, CFU-GM, that is exactly what we were doing -- or that was what was published in that PNA assay from 1992. And instead of seeing an enhancement, there is a suppression. So it's 180 degrees different. The one that he was talking about, the CFU-GEMM, which is a relatively immature human precursor that the mouse -- well, it's hard to assay that in the marine model, but they ostensibly have one. But anyway, you could see across the board there is suppression; there is no enhancement. So it is very different than what was reported in the '92 paper.

Q. Okay. And do you think the '92 paper in any way can be read to support Dr. Smith's opinion about the cell of origin of APL?

A. That's a huge stretch.

Q. Okay. And when Dr. Smith was asked about this apparent inconsistency, he said --

MR. GRAY: And this is from the rough transcript. I don't have a page number, your Honor.

BY MR. GRAY:

Q. "We were not counting the cells. We were actually looking as to whether they would form colonies in 14 days.

"Question: And you found a decrease?

"Answer: Right.

"Question: And that's the opposite of what Irons found in his study, correct?

"Answer: Well, Irons found that they were being transferred from being quiescent, from being non-dividing, into being dividing. So they could still divide and then die out.

"Question: Well, they could, but we don't know?

"Answer: We don't know. But Irons was specifically looking at a step from going from" -- we call it "quiescent to dividing. We were looking at whether they could divide and do they keep growing.

"Question: And you don't know whether they simply divided or remained alive or --

"Answer: Right. In the Irons study, you don't know that."

Were you using the same assay in the -- or was the Irons group using the same assay in its paper in '92 that the Smith

group was using in the Lan paper?

A. Dr. Smith must just not have read that Irons paper very closely, because this is wrong. We were doing exactly the same thing. It's a two-week, 14-day assay. We were looking at how cells respond to growth factors and form colonies. It takes them two weeks to form a colony that's big enough to recognize a diagnosis that you can count on.

It's a standard hematopoietic assay. People do it all over the country. They're identical assays from what was reported in the Lan paper in 2004 and what we were -- or the Irons group published in 1992. It's humans versus mice, but the growth factors were the same; the assay was the same.

Q. Okay. So to sum up on cell of origin --

MR. GRAY: If we could go back to the PowerPoint slide, your Honor.

BY MR. GRAY:

Q. You gave us your opinion in your initial report and you cited Jandl; Dr. Smith severely criticized you; you've looked at the literature again; you've looked at the papers you found; you've looked at the paper Dr. Smith found. And then he showed up at the hearing with another paper by Irons in '92. Has your opinion changed at all from the opinion you rendered in your initial report about the cell of origin for APL?

A. It hasn't changed. I think because of that criticism I have gathered more recent support for that. But I think Jandl

was correct, and the papers that he used to support it, as well as those that have been published since then, are all pretty consistently pointing to APL is arising at a more differentiated cell type than other subtypes of AML.

Q. Okay.

A. That's a long-winded answer. The answer is no, my opinion has not changed.

MR. GRAY: Your Honor, we had inquired about the possibility of an early break.

THE WITNESS: I'm fine.

MR. GRAY: Okay. We'll keep going, then.

THE WITNESS: Thank you, though.

BY MR. GRAY:

Q. Okay. Let's go to the next slide, please. So we're moving on from cell of origin. Everybody's probably happy that we're done with that for a while.

Point 2, the second part of Dr. Smith's hypotheses about biological plausibility which I stated earlier as because benzene can cause some chromosome abnormalities, it therefore can cause the 15;17 translocation. Have you looked at whether or not benzene can cause the 15;17 translocation?

A. Yes.

Q. And what have you found?

A. Well, I mean, I followed that literature very closely. And there's never been a report of benzene causing the 15;17.

Q. Okay. And as Dr. Bennett described earlier, this slide says, "Over 90 percent of APLs involve the 15;17 translocation." I believe Dr. Bennett had a number around the 97 percent range. Do you disagree with Dr. Bennett's testimony about that?

A. No.

Q. Okay. Is that something you probably would defer to Dr. Bennett on?

A. I would.

Q. He may not be an expert on everything, but he's an expert on clinical hematopathology?

A. I wouldn't argue with his opinion on how many APLs have the 15;17, if that's what you're asking me.

Q. And of course that other small percentage, whatever it is, of APLs that don't have 15;17, researchers have concluded they involve a translocation of some type at Chromosome 17, correct?

A. That's correct, which is pretty interesting to hear that.

Q. Okay. Let's go to the next slide.

This paper is by McHale, but actually, Dr. Smith is an author, correct?

A. Yes.

Q. And what was Dr. McHale, Smith and others -- it looks like about 12 them -- what were they looking for in this McHale paper?

A. There's been a whole series of these studies that Dr.

Smith's group, the various members, have published through the years looking at which cytogenetic abnormalities seem to be related to benzene exposure. And this is just the latest one in that series. But in this one they specifically address the 15;17. And they find one in the unexposed and one in the exposed and reach a conclusion that it doesn't really say much one way or another.

Q. And Dr. Smith, as you've said, he's conducted other studies of cytogenetic changes in benzene-exposed subjects, right?

A. Yes.

Q. Okay. And so far neither he nor anyone else has found an increase in t(15;17) in benzene-exposed populations?

A. That's certainly based on the published literature, yes.

Q. And let's go to the next slide. Now, this is Dr. Smith's counter to the hard evidence that no one has found t(15;17) in benzene-exposed workers. And I'll read it. Dr. Smith says, well, "APL is characterized by a chromosome translocation involving Chromosome 17 and a partner chromosome in which the two chromosome pairs undergo double-stranded breaks and rearrangement. Since benzene is a clastogenic and has the capability of breaking and rearranging chromosomes, it is biologically plausible for benzene to cause this cytogenetic abnormality." I'm not going to read the rest of it, but that is a part of Paragraph 28B of his report.

MR. GRAY: If we could go to the next slide.

BY MR. GRAY:

Q. So can you lay out for us your understanding of Dr. Smith's argument and then what some of the evidence is on this point?

A. Well, I think we pretty much have gone over that. I mean, I think, in essence, what he's saying is that, since benzene exposure has been associated with a balanced translocation, then any balanced translocation is now fair game and possible for benzene to cause. And it's related to an increase in the translocation between 8;21 that he reported in one study but then didn't see it in another study, but then he also saw a translocation between Chromosomes 14 and 18, which are relevant for this discussion because it's a lymphoid marker. But he has shown that balanced translocations occur with a 15;17. However, there is no evidence that that happens.

And he discussed on Tuesday that he doesn't think that benzene causes the 11q23 translocation any longer, which had quite a bit of relevance to the topoisomerase-inhibition argument. But at this point this indicates that that clearly is not true, that just because you can cause one balanced translocation you are not going to be able to cause all of the other ones that exist.

Q. Okay. Let's go to the next slide.

Now, this is a 2005 paper by Dr. Zhang, but I believe Dr.

Smith was also an author of the study. What did the Zhang paper find with respect to the metabolites of benzene's ability to cause some chromosomal abnormalities? And you don't necessarily have to read it, but tell us what they found.

A. I don't recall what was in that paper. I'd have to get it out and look. I mean, essentially they were looking for trisomy 8 and others. At the end Dr. Smith and his co-authors basically concluded that 5 and 7 seemed to be consistently reported associated with benzene. He doesn't think, based on this, that trisomy 8 probably has anything to do with it. I think what he says, "Thus, if hydroquinone and benzenetriol," the BT, "do selectively damage certain chromosomes in giving rise to benzene-induced leukemia, they do so by selectively causing loss of Chromosome 5 and 7, rather than a gain (trisomy) of Chromosome 8."

Q. Okay. Let me ask you a question there: Yesterday -- and we were at the end of the day with Dr. Bennett, but he had a slide up that talked about alkylating agents as opposed to topo II inhibitors. Do you recall that testimony?

A. Yes.

Q. And alkylating agents also tend to cause the chromosomal abnormalities at 5 and 7; is that fair?

A. They do, in a large proportion of cases, which is why lots of researchers through the years, including Dr. Smith, have reasoned that while benzene is not a classic alkylating agent

like some of the chemotherapy agents are, it seems to be acting in that manner causing leukemia because you do consistently see the 5 and 7 elevated across a lot of studies.

Q. So in this 2005 paper Dr. Smith is pointing to evidence that benzene acts similar to an alkylating agent, and that's possibly how it causes leukemia?

A. Absolutely. I mean, you're not going to see changes in Chromosomes 5 or 7 if the mechanism of activity is topoisomerase inhibition. That is a different path; those don't cross over.

Q. Topo II inhibitors cause other types of --

A. They do. They rarely, if ever, will be related in changes in Chromosome 5 and/or 7.

Q. Okay. Is the most important piece of data refuting Dr. Smith's argument or hypotheses about cytogenics the fact that benzene hasn't been shown to cause the t(15;17) translocation?

A. Well, I think that is an important point. I mean, I think, in all fairness, you have to point out that it's only been looked for once, but it certainly was not consistent with his theory. Yes, that is important, but that's really about as far as you could go with that.

Q. Okay. And then the second part is it's not established that just because an agent can cause one translocation, that it therefore causes all of them?

A. Yeah, absolutely that's not true.

Q. Okay. Let's go to the next slide. And again, taking a step back, we've now talked about the first two of Dr. Smith's three hypotheses about biological plausibility. We've talked about the cell of origin. We've talked about the evidence relating to chromosome abnormalities.

This third topic is admittedly a little more complicated, perhaps. But here in Paragraph 28C, I'm going to read just a little bit of Dr. Smith's topo II inhibition argument where he begins by saying, "It is biologically plausible that exposure to benzene actually induces the chromosome translocations that result in APL through the inhibition of an enzyme called topoisomerase II," which from now on we'll call topo II.

And if we could go to the next slide, please. Here you've summarized Dr. Smith's basic hypotheses and the lines of evidence. Can you walk the Court through those with specific attention to how we're going to address each of these four lines of evidence?

A. Sure. I'll try. And this is of critical importance to Dr. Smith's biological plausibility argument. I mean, if benzene is not acting as a topoisomerase inhibitor -- and by that, that is the way to induce leukemia -- you're not going to get APL. So this is fundamentally important to really what he is -- he's professing. And basically what he's saying is that some topoisomerase inhibitors cause APL, benzene metabolites inhibit topoisomerase II, so therefore, benzene probably causes

APL. So that's kind of the line that he's drawn. And we'll discuss that not all topoisomerase inhibitors are known to cause forms of leukemia. And even Dr. Smith's testimony on Tuesday really focused down this -- the mechanism by which it inhibits topoisomerase II. And we'll have to discuss that.

"Evidence regarding the mechanism of inhibition of topo II by benzene metabolites is conflicting." That's the paper that I was involved in, and some from the University of North Carolina. And it may inhibit the enzyme, but that may not be a viable pathway to leukemia. So we can discuss that.

"Benzene does not cause the predominate cytogenetic lesion associated with topoisomerase II-induced AML." That's pretty important. The most common cytogenetic change that you would expect to see in a person who has leukemia following treatment with topoisomerase II therapy is 11q23. That is a predominate -- in 100 studies across the board that is the predominate cytogenetic change. And Dr. Smith has never shown 11q23, and then discussed on Tuesday some unpublished data that he basically doesn't think it happens that way.

So now not that it's inhibiting topo II, but that it's inhibiting topo II in a very specific manner, a manner that is different from classic poisons like etoposide that do cause 11q23, it has to be doing something different. The bottom line is all of this remains an unproven hypothesis, and Dr. Smith freely acknowledges that this is a hypothesis.

Q. In his published peer-reviewed papers he acknowledges that?

A. That is my understanding, yes. Well, that -- I mean, I don't think anyone will argue that benzene metabolites under certain conditions can inhibit the enzyme. So that has gone beyond an hypothesis. But that that is a critical step in the development of a benzene-induced leukemia, that is a hypothesis.

Q. Thank you for the clarification. Yes. Okay. Let's go to the next slide.

Here we've got some topo II inhibitors that we're exposed to every day. And I want to ask you specifically about three of these. First, in the upper left corner, ciprofloxacin. Perhaps we can just call it "cipro" for the rest of this testimony. Tell us about Cipro.

A. It's a broad-spectrum antibiotic that's been shown to inhibit topo II. And there are fibro flavonoids that are in the vegetables; there are all of these naturally occurring chemicals in wheat bread and green tea and soy, soy milk, tofu. You know, they're all over the place. Topoisomerase II inhibitors are a natural part of our diet.

Apparently, if anyone has ever shown that a chemical can inhibit topo II, someone else has come along and said, well, maybe it causes leukemia. So there does seem to be a natural process, and I guess by definition, you know, that that's

something that someone should be considering. But that was the purpose of this slide, just to show that there's a lot of different things out there that cause topoisomerase II inhibition in the lab.

Q. And in your opinion, do all of these topo II inhibitors cause leukemia?

A. No. No, there's certainly no solid support for any of that.

Q. Your kids are still eating fresh vegetables?

A. Well, not often, but --

(Laughter.)

THE WITNESS: Not because of the topo II inhibition is not why they don't eat it.

BY MR. GRAY:

Q. You continue to advise your children to eat fresh vegetables?

A. Yes.

Q. Fair enough. I was rushing through that slide. Thank you for the overview.

Let's go back to Cipro. Has it been established that Cipro causes leukemia via topo II inhibition?

A. I don't think that one has even been suggested. I don't think I've seen anyone say "maybe." But there might be a paper out there where someone has said "maybe." I don't know.

Q. So that's a piece of evidence that tends to disprove Dr.

Smith's hypothesis that all topo II inhibitors cause AML, correct?

A. I don't think Dr. Smith ever said that, that all topoisomerase II inhibitors cause leukemia. But it illustrates the point that you've got to know a lot more; that simply because something can inhibit topoisomerase II does not get you to the fact that it's going to be leukemogenic. That's not the point.

Q. Okay. Fair enough. Let's talk next about Extra-Strength Tylenol which contains acetaminophen. Is there a metabolite of acetaminophen that's been recognized as a topo II inhibitor?

A. Yes, by Neil Osheroff's group at UNC.

Q. Do you think it's been established in the scientific community that Tylenol causes leukemia in people who take it?

A. That's a really big deal. Just like Dr. Garabrant said yesterday -- I think it may have been yesterday -- I mean, there is a paper that Dr. Smith pointed out where someone said that maybe -- maybe Tylenol increases the risk of leukemia, but that is very speculative. It's really premature. And I think if anyone seriously thought that Tylenol, acetaminophen, causes leukemia, we would have heard about it.

Q. Do you think the folks at the NTP that we heard about the other day, or maybe the FDA scientists, believe that Tylenol caused leukemia?

A. I think the FDA would for sure. I don't know whether the

NTP would sit up and take notice of that or not because they have a relatively specific function. But I know the FDA would be keenly interested in that. And I'm sure they reviewed that paper from 2006 and came to the same conclusion that I did, that it's a hypothesis-generating paper at best.

Q. Okay. I could have gone to the Walgreens or the CVS and done it, but I didn't. But you could go get Tylenol off the shelf today?

A. Yeah.

Q. No black box warning about leukemia?

A. No.

Q. Okay.

MR. GRAY: Let's, if we can, go to the ELMO, your Honor, briefly, and look at --

BY MR. GRAY:

Q. This is a paper by Dr. Weissa's group, "Opposing Effects of Aspirin and Acetaminophen Use on Risk of Adult Acute Leukemia," correct?

A. Yes.

Q. And I want to look at the table here that analyzes the data. Can you describe for the Court the importance of finding a dose-response relationship when you're assessing the toxicity or carcinogenicity of a particular substance?

A. I don't think the importance of that can possibly be overstated. I mean, that is a fundamental principle upon which

the whole field of toxicology is based. And that's why I feel relatively safe in saying that, at best, this is a hypothesis generation; this certainly does not prove really anything.

Q. Okay. And we're looking at a table -- I believe it's Table 3 -- where they analyze the cumulative acetaminophen use. And this is down there on the fourth row of data, I would say. And over to the right there are adjusted odds ratios for moderate use and high use. What did this paper find about people who took a lot of acetaminophen as opposed to people who just took moderate amounts?

A. Well, yeah, let's just discuss that whole table. So that table really is looking at acute leukemias. So they have not separated out myeloid versus lymphoid. And in the never-ever category, there was an increase from 1.0, which was the reference group, never, to 1.53, which was statistically significant, which is what's in the abstract. But then when you look at the data, based on the frequency where it's 1.75 or 1.74 to the duration -- and that doesn't change. The duration of use doesn't change -- the cumulative exposure actually goes down. So no measure of a dose response really indicates any change increase in the risk.

I mean, almost by definition that means that there is some other confounder. There's something else in there that is causing that first risk that is not acetaminophen. I mean, almost defintionally that's what that would indicate.

Q. Okay. And in the conclusion -- did the authors of this paper recommend that we should sound the alarm and stop taking Tylenol because, like other topo II inhibitors, it causes leukemia?

A. No.

Q. In fact, on the last page there -- I don't think we need to read the whole quote -- but did they say further research is needed?

A. Yes.

Q. And you would --

A. Appropriately so.

Q. I apologize for interrupting.

A. That's all right.

Q. Okay. Let's look on the ELMO at another one.

What is it in fresh vegetables that is an alleged topo II inhibitor? Or are there many substances?

A. Yeah.

Q. Is genistein one of them?

A. That's one that some people have discussed. But there are lots of other -- isoflavonoids and flavins and bioflavonoids and other things that share a common structure with established topoisomerase inhibitors that probably would be topoisomerase inhibitors at sufficient doses. But genistein, yes, that's one of them that has been suspected.

Q. Okay. And in Dr. Ross's paper, "Maternal Exposure to

Potential Inhibitors of DNA Topoisomerase II and Infant Leukemia," a report from the Children's Cancer Group, Dr. Ross's study found that for fresh vegetables -- and this is, I believe, for pregnant woman who --

A. Yes. Prenatal.

Q. So they're measuring leukemia in their children based on what they ate or drank while they were pregnant, right?

A. Correct.

Q. So for Table I, women who had higher intakes of fresh vegetables -- or who had fresh vegetables four to six times a week or daily -- what did Ross and those researchers find?

A. The reason why these papers are important is because I think what Dr. Smith said on Tuesday was that he was surprised by the examples that I put forth that things that inhibit topo II are not leukemogenic. And he said that there's a very strong link -- I don't remember his exact words, but there's a strong link, or very strong link, between genistein in the diet and acute infant leukemia.

And I just felt like we needed to look at the basis for that statement, and this is it. This is a paper that Julie Ross published in 1996 where she found an extraordinary risk of infant AML highlighted there 14 -- a 14-fold increase -- or a 13.7-fold increase associated with eating fruits and vegetables.

Well, that just boggles the mind. I mean, no one accepts

that. But that generated this kind of discussion within the literature, well, maybe it's genistein. Fresh fruits and vegetables have genistein in it. Genistein is a topoisomerase II inhibitor. And it's even more complicated than that. And maybe there's some truth to it. But there are other papers that have tried to reproduce this and have looked at fresh vegetables in infant leukemia and found the exact opposite effect, that it is totally protective. So whatever this is saying, it's extremely preliminary.

Q. Okay. And these same researchers, for example, found that soy, which contains genistein, in the box in this same table, did not reflect increased incidence of leukemia, correct?

A. Well, that certainly argues against it having anything to do with genistein because soy and tofu and soy products are a really good source of genistein. So whatever it is in the fresh fruits and vegetables, it doesn't appear to be genistein or you would expect to see it in the soy category as well.

Q. And genistein is another example of a topo II inhibitor which you don't believe causes leukemia, correct?

A. Well, I don't believe that there is sufficient evidence to make that claim at this point.

Q. And the authors of the Ross paper -- and I won't ask you to read it, but I'll show it up here -- I'm losing it. Did the authors of the Ross paper say that this is a very preliminary investigation?

A. Yeah. And they highlighted "very."
Q. And the data should be interpreted with extreme caution, correct?
A. Yeah. You don't want to go out there and tell pregnant women, "Don't each fresh fruits and vegetables." I don't think anyone would accept that as a valid medical position to take.
Q. Okay. If we could go back to the PowerPoint.
Okay. So we've now talked about your opinion that it's not established that all topoisomerase II inhibitors cause leukemia. Let's go to the next line of evidence regarding topo II. Dr. Smith says it's through topo II inhibition that benzene metabolites lead to AML. Can you discuss some of the evidence on that topic?
A. Well, yeah. Like we've been discussing, I think the evidence is pretty clear that benzene metabolites, under extremely controlled experimental conditions, can inhibit this enzyme. But now it's a step beyond that, even, and it has to be inhibiting the enzyme in a pretty specific way, which we can discuss. There was some debate about what we actually reasoned, that it may be inhibiting the enzyme in a way that was not consistent with it causing leukemia, and published that paper in 2001. And then there was some disagreement in the literature that said perhaps we were wrong, but we'll get into those discussions later.
Q. Let's talk about the paper that you co-wrote with Dr.

Baker. What did you find in that paper?
A. Well, we found that it is inhibiting the activity of the enzyme, but it inhibits the enzyme before the enzyme binds to DNA. So if it is inhibiting the enzyme before the enzyme binds to DNA, it does not form what are called cleavable complexes, which means that it is not a viable mechanism for leukemia; it is not damaging the DNA. And, in fact, we reported in this paper that it actually prevented the DNA damage that you would see from etoposides.

So etoposides clearly cause cleavable complexes; it's called a topo II poison. And we reported in 2001 that the benzene metabolites prevented the etoposide from damaging the DNA. So it is inhibiting the enzyme but it is not inhibiting the enzyme by a mechanism that really is --
Q. So you're saying that different so-called topo II inhibitors cause different effects, in other words?
A. There's no question.
Q. Okay. They don't all act the same?
A. They do not all act the same.
Q. Now let's look at Dr. Lindsey's paper in the next slide.
A. What Neil Osheroff's group basically said is that they went in and redid -- they didn't do it -- but they went in and did their own set of experiments and said we are wrong, that benzene metabolites do, in fact, cause cleavable complexes, and the reason we didn't see those complexes was because we had too

much of a reducing agent in the media and some other technicalities with regard to how we set up the experiment. So you've got our paper that says it doesn't cause cleavable complexes and there's a paper that says that it does.

Q. And the reason why you got one set of findings and they got another set of findings was because of how the test was set up in the lab, right?

A. That was certainly their interpretation. We never tried to go back and confirm what they had done and escalate this further, but they clearly did it differently than we did it.

Q. Well, were either of these papers studies of tissue within the bone marrow?

A. No. These were all test tube kinds of in vitro experimentation. And I think the outstanding question remains which of those two experimental conditions most accurately mimics what one would find in the bone marrow. And no one knows the answer to that. So they could be right and it could cause cleavable complexes in the bone marrow, or they could be wrong and it wouldn't cause cleavable complexes in the marrow.

They pointed out, however, that the most common form of cleavable complexes from topoisomerase II are from poisons like etoposide. The cytogenetic change associated with etoposide and topo II poisons is 11q23, which Dr. Smith acknowledged is not likely to be associated with benzene. So we've taken it even one more step away from -- you know, just because you can

inhibit topo II, you can get to leukemia.
Q. Okay. And that's taking us now to our third point. But just to back up on the lines of evidence about Topo II, number one, not all topo II inhibitors cause leukemia; number two, the exact way in which benzene metabolites interact with topo II is not completely understood. Is that fair to say based upon the differences in these papers, how it interacts in the bone marrow?
A. I think the relevance of the two artificial systems with regard to a human bone marrow is still up in the air.
Q. Fair enough. And now we're moving into the third line of evidence about whether or not Dr. Smith's hypotheses about topo II has been proven. And that is the importance of the 11q23 translocation, correct?
Okay. If we could go to the next --
A. I had forgotten we had that slide, but yes.
Q. Okay. And so if benzene caused -- strike that.
Many topo II inhibitors such as etoposide, which you just discussed, cause the 11q23 translocation, correct?
A. I'm sorry. Say it again? Ask your question again.
Q. Do many topo II inhibitors cause the 11q23 translocation?
A. Topo II inhibitors that are known to act as topo poisons cause cleavable complexes, and in AML patients where you think their AML is most likely associated with topo II inhibitors, you see the 11q23 translocation as the most common cytogenetic

change.

Q. Okay. And at the next slide, have Dr. Smith and Zhang done some research to see if you find the 11q23 translocation in benzene-exposed workers?

A. They have.

Q. Okay. And could they find it?

A. They could not. The coworkers, Dr. Smith and others in this Zhang 2007 paper, looked for two partner genes with the 11q23, acknowledging in their abstract and other places that there could be as many as 30 different partner genes. But there are some that are more common, and these are two that are the most common. But he was not able to find 11q23 translocations in benzene workers.

And then apparently, as of Tuesday, he has done something additional that is going to be published where he confirms that that doesn't appear to be happening; the 11q23 does not appear to be associated with benzene exposure.

Q. Well, that third line of evidence on the topo II hypotheses tends to disprove the hypotheses as far as benzene metabolites don't appear to cause 11q23?

A. I think that's becoming more and more clear, yes, that benzene metabolites are not going to be associated with an increase in 11q23 translocations.

Q. Okay. And topo II inhibition is something that Dr. Smith has published extensively on -- or has published several times

about, correct? He's written about it?
A. I don't know that he has.
Q. Okay. Well, I'll ask it this way: He's discussed whether or not it's established that benzene causes leukemia via topo II inhibition in his published papers, correct?
A. He has. His first graduate student, David Eastmond, I think, was the first person who really came up with this notion based on some structure-activity relationship that maybe the benzene metabolites inhibit topo II and that's how they cause leukemia. But I don't know that Dr. Smith has published papers on it, per se.
MR. GRAY: Okay. If we could go back to the ELMO.
BY MR. GRAY:
Q. And this is just a quote out of this 2007 paper that we were just discussing by Dr. Zhang and Dr. Smith. You're familiar with this study. We were just talking about it, correct?
A. Yes.
Q. And when Dr. Smith -- and this is in a peer-reviewed journal?
A. Yes.
Q. Okay. What is -- I'll let you pour some water.
A. I'm listening. Go ahead.
Q. Can you tell the Court briefly what does it mean for a journal to be peer-reviewed?

A. What does it mean? How does it work?
Q. Yeah, how does it work?
A. Well, you write your paper; you collect your data, make sure you're right, at least that you can reproduce what you're doing. And then, like Dr. Bennett said yesterday, you shoot for the stars. You want to get it published in the best journal you can within, you know, some bounds of realism. So you don't submit everything to Science or Nature; you pick a journal that you think is -- the best journal that you think it's likely to get published in.

Then you submit it and the editor reads it, usually, and says, "No, this doesn't really match," and he'll reject it on an editorial basis, or he'll send it out for peer review. And lots of people sit on panels and do that peer-review process, which then look at the data, evaluate the appropriateness of the experiment, evaluate the appropriateness of the conclusions in relationship to the data, and then weigh in as to whether or not it warrants publication, whether it has advanced the science enough to be in the journal.

So that, in essence, is it. Then they decide yes, no, you can get it published with these revisions. You know, there's lots of alternatives.
Q. Okay. And part of that review process is the reviewers are going to look at it and sort of analyze the statements you make in the paper to make sure they're supported? Is that

roughly included in the process?
A. To a more or less extent based on the journal and based on what the function of the journal is. There are simply some that will provide more leeway in terms of your discussion portion, but...
Q. Okay.
A. Everyone will pay attention to the data, the mechanism by which the data was collected, the way the data was evaluated and the way those results were presented. That will be true no matter what the journal is.
Q. Okay. And in this 2007 peer-reviewed journal, I've highlighted some language here that Dr. Smith and Dr. Zhang and others wrote where they said, "It has been suggested that the metabolites of benzene may act as topo II inhibitors in a manner similar to etoposide and azithromycin which cause disruption of the MLL gene at 11q23 and secondary leukemias with a short latency in some patients after a high dose of chemotherapy."
Did Dr. Smith in this paper say more likely than not it's been established that benzene causes leukemia through topo II inhibition?
A. That's not what -- the way I read that, no.
Q. In 2007 when he's writing in a peer-reviewed journal, he says it's a hypothesis or a suggestion, is the word he uses, correct?

A. Yes.
Q. And do you agree with Dr. Smith that it is a hypotheses that benzene causes leukemia through topo II inhibition, not an established fact?
A. Even a step further, because we've been talking about the 11q23, and he's saying here that that may be how it's acting, and I think that's not necessarily going to be accurate.
Q. The last thing I want to do, Dr. Pyatt, is just clear up something Dr. Smith said that surprised me a little bit. His testimony, when he was asked about whether or not benzene could cause APL, he said there at -- this is a rough, but the line I'm reading from is line 18, "Before this case I didn't know it was an issue." Do you recall that testimony?
A. Yes.
Q. Do you think Dr. Smith had reason to believe there was a question about whether or not benzene causes APL before this case was filed and he saw the expert reports in the case?
A. It would really surprise me if that wasn't true.
Q. Okay. For example, you've published a paper in 2004 which pointed out on page 540 -- and I'm reading from "Benzene and Hematopoietic Malignancies" written by you in 2004. You point out that erythroleukemia, M6, is a frequently reported subtype of AML in benzene-induced leukemia. "In contrast, the incidence of M3, or APL, in those studies involving secondary leukemia after benzene exposure or treatment with alkylating

agents approaches zero." And that's something you wrote in 2004, correct?

A. Yes.

Q. And that was based upon Dour or other studies that we've discussed before you wrote your paper in 2004; is that correct?

A. Many that we've been discussing today -- or this week.

Q. And I showed you this testimony before you came in. This is testimony of Dr. Smith in the Hamman case on January 30, 2007. This case apparently involved an M6. And on page 18 Dr. Smith describes what he reviewed to prepare for the deposition. And he says he read your paper that we were just citing, right?

A. Yes.

Q. And he read it for the proposition that there is increased M6 leukemia in benzene-exposed workers; is that right?

A. Yes.

Q. And as we just looked at, the sentence that discussed M6 in your paper was immediately followed by your statement about M3 and the question that maybe benzene doesn't cause it, correct?

A. That's true.

Q. So if Dr. Smith really didn't know it was an issue about whether or not benzene can cause APL until this case, it's because he forgot that he read your paper in January 2007 before that deposition in the Hamman case. Is that a fair reading?

A. I don't know.
Q. Well, he wouldn't come in here and lie.
A. No.
Q. Or you're --
A. Or he dismissed it out of hand. I don't know.
Q. And on that note we've talked extensively at this hearing -- you've been here -- the Eastmond paper that was published in 2005 also contained the question mark about whether or not benzene caused APL, true?
A. Correct.
Q. And Eastmond is an active researcher that Dr. Smith knows very well, correct?
A. Yes.
Q. So earlier when we read his quote from his report where he said "all active researchers I know understand the concept," Eastmond, at least in 2005, had a question about it?
A. He did.
Q. And you've seen Dr. Smith's testimony where he said that table from the Eastmond paper actually was first published by Eastmond in the '90s and had question marks about APL. Do you recall that testimony?
A. I don't remember exactly what he said, but I think he said David Eastmond produced that paper in the '90s. I don't know if it made it into the publication or not.
Q. And Eastmond is an active researcher that Dr. Smith has

known since the 1990s?

A. Yes.

MR. GRAY: If we could go back to the PowerPoint to conclude.

BY MR. GRAY:

Q. Can you summarize your opinions for us, Dr. Pyatt?

A. I think basically the three things that we discussed are hypotheses. They are not proven. And that really is all there is to base his opinion that a causal relationship exists between APL and benzene. The best available current evidence supports that the cell of origin for APL is not the same as other types of leukemia, or even other subtypes of AML.

There's no scientific data currently that indicates that benzene exposure results in a 15;17 translocation, and the topoisomerase II story with benzene just doesn't really match up to a straight line between that and the production of APL. So that doesn't work either.

MR. GRAY: Dr. Pyatt, those are all the questions I have. Thank you.

THE COURT: We'll take the morning recess at this point. Let me just inquire whether we have any time problems.

MR. JENSEN: Your Honor, it is my hope -- and it will guide my cross-examination -- that we do an argument after Dr. Pyatt steps down from the stand. I can -- you know, if I have 30 minutes or more, I'm fine, but I want to argue while it's

fresh in all of our minds. And so I would like to argue today, if it would please the Court.

THE COURT: Well, let me separate the two time periods. The 30 minutes was for argument?

MR. JENSEN: For me, yes.

THE COURT: What do you anticipate your examination will be?

MR. JENSEN: I will guide my cross-examination by the argument issue, which I regard as more significant, your Honor.

THE COURT: Any views from the other side?

MR. LEGHORN: Well, I've always asked the bench what it prefers to do and how you would feel that you would be most informed in making your decision, whether you want argument today --

THE COURT: I'm sort of indifferent. I see both sides of the story. There's some advantage to doing it while it's fresh; there's some advantage to letting it absorb and perhaps read some of the materials. I might come down on both sides of the issue, and that is, hear argument now but reserve the possibility of having you back.

MR. LEGHORN: That's fine with us, your Honor.

MR. GRAY: If I may interrupt Mr. Leghorn. Would we get the opportunity to do some post-hearing briefing to address some of the issues that have been raised here? Not to raise new things, but to provide the Court with what we believe the

roadmap was over the course of the hearing? Would the Court be receptive to that?

THE COURT: I'm not sure how necessary it is. You're going to give me all the PowerPoint slides anyway. I mean, that's going to be your brief, really. I don't think we need any more briefing on things.

MR. LEGHORN: Your Honor, speaking of that, I should have copies of at least defendants' for you today.

THE COURT: I'm not going to decide it this afternoon.

MR. LEGHORN: Excuse me?

THE COURT: I'm said I'm not going to decide it this afternoon.

MR. LEGHORN: I just wanted you to know there might be a couple more pieces of paper before we finish that we'll give to the Court before we leave this morning.

MR. GRAY: Our CVs and reports that we provided earlier, those have been marked for the hearing, correct?

THE COURT: Well, they will be. I have the binder.

MR. LEGHORN: Whatever the next number is.

THE COURT: Who will be arguing for the respective sides? I gather Mr. Jensen is for plaintiff?

MR. LEGHORN: I will be, your Honor.

THE COURT: Well, I don't want you to cut short what you think is an appropriate examination, so let's see how things -- well, I understand what you're saying. We have some

time this afternoon but not a lot. But one possibility -- well, I don't know how long your examination will be. If you -- if we don't finish the witness until one o'clock, I think we can come back and between two and three and have argument. How does that sound to people?

MR. JENSEN: I think we'll be finished with the witness before one o'clock even if I do everything I ever wanted to do, your Honor, but that would be fine with us.

THE COURT: Why don't we provisionally do that.

MR. LEGHORN: Thank you, your Honor.

THE CLERK: All rise.

Court will take the morning recess.

(There is a recess in the proceedings from 11:03 a.m. to 11:30 a.m.)

THE CLERK: All rise.

A continuation of the Milward Daubert hearing.

THE COURT: Go ahead, sir.

CROSS-EXAMINATION

BY MR. JENSEN:

Q. Good morning, Dr. Pyatt.

A. Good morning.

Q. Are you aware of whether there are occupational medicine experts that take the position that benzene is capable of causing APL?

A. As a distinct subtype?

Q. Yes.
A. I'm not.
Q. Okay. Are you familiar with the --
MR. JENSEN: If I could have that ELMO, your Honor.
BY MR. JENSEN:
Q. Are you familiar with the textbook "Occupational Health: Recognizing and Preventing Work-Related Disease" by Dr. Levy and Dr. Wegman?
A. I've never seen that book. I'm familiar with Dr. Levy.
Q. Okay. You don't know who Dr. Wegman is?
A. No.
Q. There's of this chapter in this edition, the third edition of the Levy-Wegman book, entitled "Hematologic Disorders." And the chapter itself is written by Bernard Goldstein and Howard Kipen. Do you know who Dr. Goldstein is?
A. Yes.
Q. And who is Dr. Goldstein?
A. Bernie Goldstein? I think he's a retired professor of hematology at the University of Pittsburgh. But he did a lot of early work in some of -- the metabolism of benzene in some animals models, and was one of the early proponents that there was only one metabolite that may be different than the quinones. But he's been doing benzene research for quite some time.
Q. And based upon your knowledge of Dr. Goldstein, would you

agree that he is a reasonable scientist who has a background in benzene toxicity and benzene causation?

A. Dr. Goldstein has made some statements and taken some positions that I disagree with. But I think in answer to your question, by and large, yes.

And I know Dr. Kipen well.

Q. And you disagree with a lot of scientists who you consider to be reasonable scientists; isn't that fair to say, Doctor?

A. Well, I mean, yes. Scientists disagree all the time about a variety of things.

Q. Okay. And the mere fact that scientists are disagreeing with each other doesn't mean that either one of them is a bad scientist, correct?

A. Well, it depends on what they're disagreeing on.

Q. Well, the fact of disagreement alone, you would agree, does not necessitate that either one of them is a bad scientist in general, right?

A. Well, I mean, if one scientist was taking a position which is clearly contrary to the established view, and something that was completely obvious to everyone, that they were taking an opinion that was opposite, then that disagreement would indicate something inherent about that one party to the disagreement. So I don't -- I mean, your question is assuming that all of the disagreements are reasonable, and I don't know that that's right.

Q. Well, that wasn't my intent, to put that assumption into the question, Doctor. I was asking a different question, which is -- and I'll phrase it differently.

A. Okay. Maybe I just misunderstood you.

Q. Okay. It's true that reasonable scientific disagreement is an ordinary part of scientific discourse, right?

A. Yes.

Q. And many times when two sides disagree it's part of reasonable scientific discourse, correct?

A. Absolutely.

Q. All right. Now, in this chapter by Dr. Goldstein and Dr. Kipen, they have a table, which I'll try and zoom in on here. And the table says "Relationship of Benzene Exposure to Hematologic Disorders." And one heading says "Causality Proven," and it says "pancytopenia and aplastic anemia," and under that it says "acute myelogenous leukemia and variants (including acute myelocytic leukemia, acute promyelocytic leukemia and erythroleukemia)."

So Dr. Goldstein and Dr. Tipper [sic] have taken a position in this table in this chapter that benzene exposure is capable of causing APL. Do you agree with that?

A. Yes. It's Kipen, E-N.

Q. I apologize.

A. I think, yes, based on that table.

Q. And so this textbook chapter is an illustration of

reasonable scientists who take the position in disagreement with you that benzene exposure is, in fact, capable of causing APL, true?

A. Well, I think that the -- whether or not that disagreement would be reasonable, I would have to ask Dr. Goldstein or Dr. Kipen what scientific evidence they have evaluated, or perhaps it's in the citation list for that chapter. If they have evaluated all of the same scientific evidence that I've evaluated, then I think what they're saying is true. But if they haven't evaluated all of the available data, or they're making some assumptions in there that I don't think are true, then it would not be reasonable.

Q. Okay. Well, even if we don't know because we don't know what was in Dr. Goldstein's head and he's not here to testify and whatnot, whether or not it would be your view that the position taken in the chapter was reasonable with respect to benzene and APL, you do agree that Dr. Goldstein, in general, is a reasonable scientist, correct?

A. Yes.

Q. Now, are you familiar with this textbook that I'm showing everyone here by -- it's "Occupational and Environmental Medicine" textbook by Dr. Rosenstock and Dr. Cullen, are the first two authors.

A. Actually, I think they're the editors. But I have seen that textbook but I'm not familiar with it.

Q. All right. So you're familiar with its existence but not its contents?

A. Correct.

Q. All right. Just for the record, this edition of the book is the second edition, 2005. And here's another chapter. And Dr. Kipen is again one of the authors on this chapter. And it is entitled "Lymphohematopoietic Malignancies." And there's a similar table in this chapter in which Drs. Kipen and Wartenberg describe the known suspected and reported relations between benzene exposure and various hematologic disorders, correct?

A. Yes.

Q. Okay. And this table, similarly to the table we saw in the Levy and Wegman chapter, it says under "Known: Acute myelogenous leukemia and variants." And when you -- would you agree with me, Doctor, that variants of acute myelogenous leukemia suggest all the subtypes of acute myelogenous leukemia?

A. I think that would be one interpretation of it. I mean, I don't think that necessarily is true, but I think that would be one interpretation.

Q. Okay. So it is a fair -- it is at least one fair reading of this table to say that these authors had reached the conclusion that benzene exposure is a known cause of APL?

A. I think it would be that benzene exposure is a known cause

of AML.
Q. AML including all of its subtypes. That's at least one fair interpretation of this table, right?
A. It would be an interpretation, yes. It would be a fair interpretation. I mean, I think you would have to ask Dr. Kipen or look at the references. You know, based on those references, that might give you some insight into what they were thinking when they put that table together.
Q. Is it true in general, Doctor --
MR. GRAY: Your Honor, can I see the Kipen text?
MR. JENSEN: Sure.
BY MR. JENSEN:
Q. Is it true in general, Dr. Pyatt, that there are many textbooks in the field of occupational environmental medicine which mention that benzene is a known established cause of AML?
A. That wouldn't surprise me.
Q. Okay. You've seen some such textbooks, in any event; is that true?
A. In what field?
Q. In occupational medicine.
A. Yes.
Q. And you've seen statements to that effect in some of those textbooks that you've reviewed; is that true?
A. Yes.
Q. And as you sit here today can -- well, let me back up.

You've also -- you're also familiar with some hematology textbooks; isn't that true?
A. Yes.
Q. And isn't it true that many hematology textbooks have statements that indicate that benzene is a known cause of AML?
A. Yes.
Q. Okay.
A. I can think of at least two where that's true.
Q. Are you familiar with some oncology textbooks?
A. Less so.
Q. Okay. Do you know whether any oncology textbooks have statements that indicate that benzene is a known cause of AML?
A. I'm not doubting that they exist, but I'm not familiar with them, sitting here.
Q. So you've got some familiarity with textbooks, at least in the fields of hematology and occupational and environmental medicine, which state somewhere in the textbook that benzene is a known cause of AML, correct?
A. With some exposure caveats, but yes.
Q. Sure. And as far as you're aware, Dr. Pyatt, do any of those textbooks qualify that statement by saying "Benzene is a known cause of AML except for certain subvariants or except for APL"? Is that kind of language in any of those textbooks?
A. I'm not sure about the Winthrop encyclopedia, kind of, of hematology, but that language is in the Jandl textbook. I

mean, it certainly calls into attention the different support for the various subtypes, and it recognizes that these subtypes are important in epidemiology. So I don't recall exactly what he said about it, but he clearly was discussing subtype analysis within that section.

Q. Okay. But would you agree that it's fair to say that the vast majority of textbooks in both of those fields that mention benzene and AML do not qualify by subtype?

A. I'm sorry. I can't make that -- I mean, I've only looked at two, and one did and one didn't. So in my experience, 50 percent of them looked.

Q. All right. Dr. Pyatt, you're a toxicologist, correct?

A. Yes.

Q. And as a toxicologist, you have formal training and also experience in the review and interpretation of epidemiology; is that fair to say?

A. Yes.

Q. And you also have some training and experience, or at least -- "experience" may not be the right word -- but you have some training and knowledge about how epidemiologists go about the design of epidemiology studies; is that fair to say?

A. Yes. I teach an environmental epi class.

Q. Doctor, would you agree that when epidemiologists design formal epidemiology studies to test a particular hypothesis that a chemical causes -- a particular chemical causes a

particular disease, they're always going to apply some type of statistical analysis as part of that process?

A. I think the statistical analysis is going to be intrinsic in any data analysis section you're going to employ statistics to allow you to evaluate the chance -- the potential role that chance played in the data that you've accumulated.

Q. Well, even before you get to the role that chance plays, statistical analysis is part of determining whether there's an association to begin with, right?

A. Well, that is what I'm talking about.

Q. All right. So there's a -- there's statistical analysis applied to measuring an association between the exposure and chemical, correct, or the lack of an association?

A. Right. And there's probably -- I mean, there's statistical analysis used to evaluate the -- how big the study needs to be based on disease incidence and lots of other aspects of the study.

Q. Right. And so calculations -- on the association point it's measured quantitatively and it's defined differently depending on what kind of study it is, but in most cohort studies it would be a relative risk calculation; is that fair to say?

A. In those cohorts? Well, they're all relative risks at one point. Usually you would have a standardized mortality ratio or a standardized incidence ratio, but those are essentially

relative risks. So sure.

Q. And it could be an odds ratio in a case-control study?

A. Same. Same residual concept.

Q. It's all measuring the extent to which the exposure at issue is connected with the disease at issue, right?

A. Potentially, yes.

Q. And it's attempting to quantify the extent to which there may be an association. The association itself is measured by those numbers: relative risk, standardized mortality ratio, odds ratio, whatever it is?

A. It's described by those numbers, yes.

Q. And there's separate -- or in connection with measuring those associations, they also -- epidemiologists will design their epidemiology studies to do statistical analysis to attempt to gauge the likelihood that any association was due to chance alone, right?

A. Correct.

Q. And many studies will also be designed -- not necessarily all of them -- but also will be designed to do an even more statistical analysis to try to quantitatively assess whether any measured association might be due to confounding effects, correct?

A. I understand the concept of that. I don't know mathematically how they do that, how they stratify out various confounders.

Q. But, in fact, you do see language in many epidemiology studies, Dr. Pyatt, that say "We adjusted for age, sex, race," et cetera, that all of which they've done -- the purpose of which is to try and eliminate or quantitatively assess whether the association is caused by these potential confounding variables, right?

A. Or at least that the potential association is impacted upon by those various confounders, yes.

Q. And that's more math that epidemiologists are doing, correct?

A. Correct.

Q. And all of that is a quantified calculation, mathematical process that we've been talking about, that epidemiologists do when they're designing a study to test a particular hypothesis that a chemical causes a particular disease, correct?

A. Can you repeat that one again?

Q. Yeah, that was bad. We've been describing a quantified process -- a calculation process that epidemiologists go through when they design formal epidemiology studies to test the hypothesis that a chemical causes a particular disease, right?

A. Yes.

Q. And as far as you know, if that is the primary purpose of the study, to test that kind of hypothesis, that kind of statistical analysis is always part of the study design,

correct?
A. I mean, if it's a quantitative epi study, of course. It has to have math.
Q. Right. Okay. Now, given what we've just been through, Dr. Pyatt, has -- to your knowledge, has any epidemiology study ever been designed to test the hypothesis that benzene causes APL specifically?
A. I don't think there's any indication of that in the published literature. I wouldn't say that there are no studies where that was at least part of the goal that they're working towards.
Q. But you'd agree with me that, for example, the Travis study that's been discussed a lot this week, that was not designed to test the hypothesis that benzene causes APL, right?
A. Well, I don't know that they even had a hypothesis. That study was just looking at what happened in these Chinese workers that were exposed to benzene. Once you collect a group of data from doing your analysis, then you can analyze that data lots of different ways and you can formulate lots of hypotheses that are testable based on the data that you collected from that previous study.
So while that may not have been a set-out purpose of the study in the beginning, that doesn't preclude someone later from coming in and looking at the published data.
Q. Okay. But as far as it goes, the answer to my question is

yes, right, that the purpose -- the designed purpose of the study was not to test the hypothesis that benzene causes APL?

A. Oh, no. No, that was not -- that was not an express purpose of the Chinese study, no. So what you're saying is yes, I guess.

Q. And I want to clarify, I guess, because we've talked an awful lot about Chinese studies this week and we're not always talking about the same thing. We're talking about Travis right now. And Travis, just to clarify, is a substudy from the cohort -- the large cohort that was a joint -- is an ongoing joint study being conducted by the NCI and the Chinese government, correct?

A. The NCI and the -- yes. The Chinese Academy of Preventative Medicine, correct. Travis was a -- I actually thought we were talking about Hayes from 1997. Travis is fine. But that was more of a description of the types of hematopoietic malignancies and lymphohematopoietic malignancies that they observed in benzene-exposed workers.

Q. And in the Travis paper, they don't even try to measure any type of association at all quantitatively; isn't that true?

A. Yeah, that was not the intent of that study.

Q. And you would also agree that the Rinsky Pliofilm study and all the papers that came out of the Pliofilm cohort were not designed to test the hypothesis that benzene causes APL, right?

A. I would say my answer to that one would be the same as my answer to your first one, that that was not an express purpose of the study. But data has been collected that can be evaluated later that might inform a number of questions.

Q. Okay. And there was no quantified measure of association that was calculated in the Rinsky study or any of the variations on the Pliofilm cohort study that attempted to measure an association between benzene and APL, right?

A. There were none. I don't know how they could possibly do that.

Q. So is it your testimony that there were no APLs in the Rinsky cohort? Do we have to go through that again?

A. It was my testimony that there were none of them listed.

Q. That's a different statement, isn't it, Doctor?

A. Well, no. I mean, you're asking me whether or not they could conduct statistical analysis. I don't know how they could conduct a statistical analysis on something that's not there.

Q. Yes, Doctor. But you've also testified just a moment ago, twice, that people can come behind later and make inferences based on the study. And you're suggesting that you can make the inference that the Rinsky study is affirmatively evidence that benzene does not cause APL. Isn't that what you're suggesting?

A. Yeah. You've taken it about four steps further than I

did. I thought what we were saying was did they go in and conduct statistical analysis for APL and benzene in Rinsky. And my answer was no, they couldn't. There were none.

Q. And Golomb -- the Golomb paper -- first of all, the Golomb paper, you would agree, is not even a formal epidemiological study, right?

A. I would agree with that.

Q. It's a case series. Is that a fair description of it?

A. I'd have to take it out and look at the actual design, but I think that's close.

Q. In any event, there's no quantified -- there's no attempt to quantify an association between benzene and any types of leukemia, correct?

A. I need to get it out and look. I do have it, if you'd like to discuss it.

Q. We don't need to go through that, Doctor.

A. Okay.

Q. Well, as part of your opinion in this case, even though you didn't testify about -- or much about epidemiological studies in your direct examination, you did, in fact, review what you believed were the -- was the relevant body of literature with respect to the issue of whether benzene is capable of causing APL specifically in the field of epidemiology, right?

A. I did, yes. I mean, we just kind of divided up the

various sections for the purposes of this hearing. And, sure, that was not part of what I was going to be testifying on.

Q. But you did issue a -- you reviewed it and you reached opinions, in part, based on it, and you issued a report; is that correct?

A. I did.

Q. Now, to your knowledge, has any formal epidemiology study ever been published where the authors designed the study to test the hypothesis whether benzene can cause any specific subtype of AML?

A. I'd have to look, but I think the answer to that is yes. They were not very large or very strong studies, but there are a series, Mitelman and Cuneo and some others, that were interested in whether or not there were associations with various subtypes. And I think they did conduct some statistical analysis. Some of those looked at karyotypes or the cytogenics. Some of them looked at the subtyping, which we'd agree APL/15;17, those are synonymous. I would have to look to see whether they ever did any type of quantification.

Q. Now, you had reviewed those studies that you just mentioned for purposes of developing your original opinion before you ever issued a report in this case; is that true?

A. Sure.

Q. And your report in this case was issued before your deposition was taken in this case; is that correct?

A. Yeah. Yeah. Yeah. Yes.
Q. Okay. And isn't it the case, Dr. Pyatt, that at the time of your deposition you could not point me to any epidemiological study with which you were familiar in which an actual measured quantified association was discussed and reported with respect to specific subtypes of AML?
A. I don't recall exactly what I said. I was more familiar with the literature at the time of my deposition than I am now. It's been two or three weeks since I've looked at these. I mean, I know that they express data related to the various subtypes and the various cytogenics. I don't recall whether they conducted any kind of formalized statistics.
Q. All right. I'll come back to your deposition in just a moment, Doctor.
To the extent that the paper -- scratch that. I'll come back to that point in just a moment, but I want to go to a different but related point now.
Dr. Pyatt, it is your opinion that in order to reach a conclusion whether a chemical exposure is capable of causing a disease, a scientist must have consistently positive results obtained from quantitative epidemiology studies, either cohort or case-controlled; isn't that true?
A. What was the first part of that again, to absolutely establish that a chemical can cause disease? Yes, you need quantified epidemiology that has been reproduced.

Q. In order to reach a conclusion on general causation, you need consistently positive results from quantified -- quantitative epidemiology studies, correct?
A. Before you can establish that a chemical definitively causes disease, yes.
Q. And when you say "consistently positive results," you're talking about two or more positive results from separately conducted epidemiology studies, right?
A. I think that would be close to the minimum.
Q. So, Dr. Pyatt, isn't it true that in your opinion based on the state of the epidemiology with respect to benzene and specific subtypes of AML, that it is your opinion that it is not possible to reach with certainty an opinion that benzene causes any subtype of AML?
A. Because of the quantification; is that what you're saying?
Q. That's what I'm saying.
A. I'm not sure that I would go that far.
Q. That's, in fact, what the logic of your position is in this opinion, isn't it?
A. Well, no. I mean, you need to be a little -- you would rely -- for other subtypes you would rely on the quantitative epi for benzene and AML. So if you were asking me questions about M1 or M4, there doesn't have to be a specific study saying, "We've looked at M4 and it is statistically elevated." The reason why this one is different is because of what we've

been talking about this week, that APL is a very distinct subtype. So that's --

Q. So all the subtypes are different from one another but APL is more different than all the rest; is that your testimony?

A. Yes.

Q. And for that reason you get to treat APL differently, and the AML and benzene literature has nothing to do with APL even though it does prove, by itself, that benzene causes all the other subtypes. That's your testimony, right, Doctor?

A. I didn't follow all that.

Q. You've told us, Doctor, that it is your position in general that in order to establish a relation between a chemical exposure and a disease, it is a sine qua non; you've got to have consistently epidemiological studies that quantify an association between the chemical exposure and the disease at issue, correct?

A. Consistently positive? I think you need to do a weight-of-the-evidence evaluation. But, yes, in general I think that's true.

Q. So the answer to my question is yes?

A. Yes.

Q. All right. And there are no -- as you sit here today you cannot point to any quantified consistent epidemiology associations between benzene and any specific subtype of AML; that's true too, right?

A. I think that's true, yes.
Q. But in spite of your general position that you cannot associate a chemical with a particular disease in the absence of quantified consistent positive epidemiological evidence, and the fact that we don't have that kind of evidence for benzene subtypes, you're still -- AML subtypes. Excuse me -- you're still taking the position that it is possible to establish that benzene causes other types of AML besides APL, right?
A. Well, it's different. It's different because APL has been -- acute promyelocytic leukemia has been recognized as a clearly distinct, unique subtype, and people have looked at it independently. I don't know of anyone who has looked for an M5 independently, or at least to the extent they have with APL. In the future this may not be true. Other subtypes may be evaluated.
Q. Isn't it true, Dr. Pyatt, that every subtype of AML has specific morphological, cytogenetic and molecular genetic profiles that differentiate it from the other subtypes?
A. Say that again?
Q. Every subtype of AML, all eight of the different separate FAB subtypes --
A. Yes, they have differences for sure.
Q. They all have differences that are unique to them that separate them. That's why they're their own subtype, right?
A. Correct.

Q. But you're saying, oh, the fact that they're different from each other doesn't matter except when we're in the courtroom to testify about APL?
A. No, I'm not saying that at all.
Q. APL is more different than all the other ones. That's what you're saying, right?
A. Clearly.
Q. And you'd agree with me that they all have specific morphologic, cytogenetic and molecular genetic profiles that differentiate them from one another, right?
A. All the different subtypes of AML?
Q. That's my question.
A. Yes.
Q. Now, Dr. Pyatt, based on your view that you need consistently positive results obtained from quantitative epidemiology studies in order to make a connection between a chemical exposure and a disease, isn't it true that no matter how strong any of the mechanistic evidence you've been talking about in your testimony today was, it would still be your opinion that you cannot say that benzene causes APL, right?
A. Well, I mean, if there was a really strong plausible mechanism that was a pretty straight line from benzene to APL, accounting for the fact that APL is really very different from the other subtypes, I'm not sure. I'm not sure how that would play out.

Q. So your requirement for epidemiology is a requirement except when it's not a requirement?
A. I don't know how to answer that.
Q. When -- if -- do you mean it or not? Does epidemiology have to be present or does it not have to be present, necessarily?
A. Well, I mean, I think if you took the position that APL was not that much different than the others, if there was no strong scientific support for the fact that you need to look at it separately, then there would be no reason to assume that it would not be like the other subtypes, and then you would be relying on the quantitative epidemiology that exists for AML as a collective grouping.
Q. I want to move for a few minutes, Dr. Pyatt, to the issue of what we've been describing as cell of origin. And I'm going to pop up on the screen -- before I do that -- all right. I'll go back to that.

MR. JENSEN: My apologies to everybody.

(Pause.)

BY MR. JENSEN:
Q. So, Dr. Pyatt, you agree that this is a fair representation of how blood cells develop?
A. Yes.
Q. And we've struggled a little bit -- I think some of the witnesses have said -- with the nomenclature about what stem

cells are, what progenitors cells are, et cetera. As I understood your testimony, at the top we've got what you would call a stem cell, correct?

A. Yes.

Q. And as we get lower, we've got what your -- you would describe anything past that level as a progenitor cell until we get to the committed cell level down here, right?

A. No.

Q. No? Okay. These are progenitors, correct?

A. Yes. The committed part was what you had wrong.

Q. Okay.

A. Right there where your finger is, that's where it makes the first commitment decision. So it is lineage-committed beyond that point.

Q. Okay. So when we go over to CMP, that means it's committed to myeloid cells only, correct?

A. Correct.

Q. And CLP is committed to lymphoid cells only?

A. That is correct.

Q. And you agree that there are a group of reasonable scientists who reasonably believe that all forms of AML arise from the same progenitor cell, correct?

A. All forms of AML?

Q. AML.

A. I've seen that language in several studies. I've never

seen anyone who writes that include APL as part of their distinct description. But by and large, yes, I think that's true.

Q. In fact, you testified at your deposition that reasonable scientists not only could disagree, but they do disagree, and you facetiously said that experimental hematologists get into fist fights over the issue, right?

A. Over the cell versus the different subtypes; yes.

Q. And some believe that it's a common cell of origin for all AMLs, right?

A. Yes.

Q. And as far as you're concerned, that's an area where reasonable scientists can and do disagree?

A. I think that is consistent with most of the evidence.

Q. So that, in your view, is a matter of scientific judgment to determine whether the weight of the evidence supports that all of the AMLs start at the same cell of origin or not?

A. Well, I don't -- I mean, the Wojiski paper is pretty important, and I think that will go a long way toward if people do still believe what you say is true -- not you personally, but this proposition that they all come from the same cell of origin -- I think that paper will go a long way towards pushing people off of that.

But as Dr. Bennett pointed out yesterday, there are other forms of AML with an 8;21 translocation and monocytic and other

things, that seem to indicate that those occur at more differentiated cells. So you can find it in the literature. I haven't ever done a survey of experimental hematologists to find out where they are on this, but you would probably find some that adhere to what you said.

Q. Well, in fact, you testified at your deposition that they disagree about this issue all the time, right?

A. Right. And because of that disagreement people continue to do experiments and form the decision -- or then form the question, and then they're evolving.

Q. With respect to the Wojiski paper specifically, Dr. Pyatt, that paper was only recently, within the last few weeks, made available online, correct?

A. I think that's right. It was 2009. I don't recall when it came out.

Q. So in any event, any time in 2009, it would be after Dr. Smith's opinion -- original report in this case, correct?

A. Yes.

Q. And after his supplemental declaration in this case, right?

A. I think so, yes.

Q. And it would be well after the mid-1990s when Dr. Smith said he originally reached his opinion on the subject of whether benzene causes APL, right?

A. What? I lost your question.

Q. I asked you a chronological question. I'll withdraw it.

The point is, though, you agree that Dr. Smith could not have considered Wojiski in making his assessment and review of the scientific literature to reach a weight-of-the-evidence judgment as to whether benzene causes APL?

A. No, not before the paper came out. But I -- he did -- he did read it and understand it and take it to heart, and I think he's persuaded by that data. So I think now he would probably say, based on that, that the different subtypes of AML are probably not occurring at the same level. I don't know that he would say that or not, but that certainly would support that proposition.

Q. Are you telling me you heard his testimony on Tuesday and that's what you gleaned from it? Really?

A. Well, what I heard him say on Tuesday was that this was a complicated paper and it was new, but that he found it important.

Q. Don't you remember him saying that this does nothing to show that APL cannot and does not also begin at higher levels where the -- for example, the CMP level is represented on this chart -- where all of the different cell lines of AML are -- can be differentiated from -- descend from?

A. Well, I think the authors themselves say that their data does not rule out that possibility.

Q. And, in fact, didn't you hear Dr. Smith say that he still

believes it's possible that all forms of AML, including APL, can and do begin, at least in certain instances, from a common stem or progenitor cell?

A. I mean, the discussion -- the disagreement that I had with Dr. Smith from the very beginning of this process was when he took the position that all forms of leukemia -- all forms of leukemia, not subtypes of AML, but all of them -- come from the same stem cell, the pluripotential stem cell. And that is originally what I wrote on my report. I said I don't believe that. I don't think that is supportable by the scientific evidence.

What I heard him say on Tuesday was that he had backed off that, and it was stem and progenitor cells which encompasses a whole lot of different things. So I think he has changed his view somewhat on that particular issue.

Q. But he still maintains that all -- even under your interpretation, Dr. Pyatt, you agree that Dr. Smith testified on Tuesday -- and of course the transcript will show what he really said, but your interpretation of that -- isn't it true that a fair interpretation is that you believe that at the very least all AMLs, including APL, can and do at least sometimes develop at the CMP level or higher on this chart?

A. What do you mean by "can"? That they sometimes do and they sometimes don't?

Q. Correct.

A. Yes.
Q. Okay. You agree that the hematopoietic progenitor cell -- and by that did you mean about this level, Dr. Pyatt?
A. No.
Q. Okay. What did you mean --
A. Well, hematopoietic is a blood cell, so that's any of these.
Q. Okay.
A. And a progenitor cell is anything that's not a stem cell.
Q. Okay. All right. Now, would you agree that a hematopoietic progenitor -- I apologize. Go ahead.
A. Experimental hematologists use "progenitor cell" typically to describe a population of cells that are CD34+, and because of that antigen, CD34, that allows us to collect that population of cells and do things with them. Those are called hematopoietic progenitor stem cells; they are used as therapy for stem cell transplantation and they will include all of these mature and immature progenitors that are depicted on this slide.
Q. And the hematopoietic progenitor cells target tissue for benzene toxicity, correct?
A. I believe so, yes.
Q. And there are reasonable scientists who believe that this damage caused by benzene or its metabolites at the progenitor cell level is what ultimately leads to the development of AML,

correct?
A. Yes. And people have been, for decades, trying to understand what exactly mechanistically is happening in these progenitor cells.
Q. And now, Dr. Pyatt, if we assume that benzene causes AML, at least in part by causing damage at the progenitor stem cell level -- so we've got that assumption, I'm asking you a hypothetical question. So my first assumption is for you to assume that benzene causes AML, and part of the mechanism, at least, is damage caused at the progenitor cell level. Do you understand me so far?
A. Okay. Well, the first time you said "progenitor stem." That time you left out the word "stem."
Q. I apologize for that. I didn't intend to insert the word "stem."
A. Okay. So at progenitor cell level. Yes, I agree with that.
Q. And if we also assume that all subtypes of AML start with damage at the same progenitor cell, then you would agree that this would be some evidence that benzene exposure is capable of causing all forms of AML, right?
A. In your hypothetical world if that was the only piece of information we have, yes, there would be no reason to doubt that.
Q. Well, whether or not it's the only piece of information we

have, it is some piece of information that supports that hypothesis, right?

A. Would support that hypothesis. But if the overwhelming weight of the evidence is on the other side, then you still wouldn't think that that's a logical step.

Q. You agree that when experts assess whether a chemical is -- chemical exposure is capable of causing a particular disease, that the expert reviews the body of data that appear to bear on causal judgment; select the scientifically relevant data; assess and weigh studies for their qualities; weigh the importance of different kinds of data vis-à-vis one another, for example, animal studies versus human studies versus short-term studies versus structure activity relationships versus mechanistic evidence versus any case studies and so on; and brings her background understanding of biology and toxicology as well as her understanding of the phenomenon to the causal issues. You agree with that, right?

A. Yes.

Q. And, in fact, when you talked about your view based on the weight of the evidence that benzene does not cause APL, that involves the process that, you know, you just described in that question, right?

A. It involves the process. It doesn't necessarily include all of the things that you listed, because there's many things that you listed that don't have sufficient data to really

inform this question.
Q. And when you apply that kind of -- and we could broadly agree that that process has been generally described as being a weight-of-the-evidence evaluation, right?
A. Yes.
Q. And when you do your overall weight-of-the-evidence evaluation in this case, it is your scientific judgment that the other evidence outweighs any evidence as to whether all AMLs develop from a common origin, right?
A. I'm sorry. I didn't get the "my judgment" part. Can you just repeat the question?
Q. Okay. When you do your overall weight-of-the-evidence evaluation, you're basing on your scientific judgment your view that there is other evidence that outweighs any evidence that all AMLs come from a common progenitor, right?
A. Let me see if this works. I have evaluated all of the relevant scientific data that I know to exist, and it is my opinion that it is the most consistent with the position that the subtypes of AML are not arising in the same cell. Is that what you asked?
Q. And you had to use your scientific judgment to come to that evaluation. That's all I'm really trying to get at, Doctor.
A. I think my experience and expertise and understanding of the science helps. I don't have a piece that says this is the

judgment and I'm going to use it now. I mean, I don't know what that means.

Q. But you had to apply judgment. You're not disagreeing with that, right?

A. You mean like this paper is no good, there's really nothing that I could use here? I think that plays a role, yes.

Q. Would you agree, with respect to your discussion of cigarette smoking and APL, that Dr. Smith reviewed the same body of epidemiological literature that you had and came to a different interpretation?

A. No. I don't know what -- I don't know what Dr. Smith reviewed.

Q. In fact, he describes in his supplemental declaration at least a portion of what he reviewed, does he not?

A. But it didn't include all of the studies that we discussed today.

Q. First of all, before I even get to what Dr. Smith had to say about this subject in his supplemental declaration, you testified on direct that, in fact, some of these studies on cigarette smoking and specific subtypes of AML, the authors themselves say that this is a very fuzzy area, right?

A. With regard to the cytogenics, yes.

Q. I've put up on the ELMO the supplemental declaration of Dr. Smith. And he says, "A careful review of the literature on the cytogenic subgroups of AML found in cigarette smokers

reveals no clear association between smoking and cytogenetic subtypes of AML." Then he goes on from there and he describes studies that he reviewed including the Moorman paper that you looked at today, right?

A. Yes. He does have all three of them there.

Q. So based on that, you would agree with me that you looked at the same body of literature and came to a different conclusion, right?

A. Apparently.

Q. And, in fact, you don't have any quarrel with the method of reviewing the literature and then reaching inferences from the evidence that's available in the literature to determine what your opinion is. That's how it works, right?

A. Yes.

Q. On topoisomerase, Dr. Pyatt, you agree there is a well-established body of data to show that benzene's metabolites inhibit topoisomerase II in human cells at least under certain conditions, correct?

A. Yes.

Q. That's been reported repeatedly in the literature, right?

A. Correct.

Q. And your opinion is that the weight of the evidence does not provide sufficient evidence to conclude that this actually happens -- the inhibition of topoisomerase actually happens -- in benzene-exposed people, but you don't think there's enough

evidence about that, right?
A. Well, there's no evidence about that. It's not my opinion that there's some or there's not; there is no evidence to support that, period.
Q. Well, Dr. Pyatt, don't you agree that reasonable scientists reviewing this same body of data have concluded that benzene's metabolites probably do inhibit topoisomerase II in human beings?
A. That's a different question. I mean, they can think that it might or that it probably does based on a hypothesis, but there's no evidence that it does.
Q. "Reasonable scientists have inferred from the data that benzene's metabolites probably do inhibit topoisomerase II in human beings," right?
A. That is a hypothesis.
Q. No. It's a hypothesis that reasonable scientists have reached that conclusion?
A. What they're reaching is a hypothesis. And keep in mind that that is not -- I mean, there's data now that David Eastmond published that shows that benzene exposure does cause inhibition within the bone marrow of those highly exposed experimental animals. So whether it happens in the bone marrow, I think, is becoming less of an issue. But there is still no data showing that this is occurring in the bone marrow of benzene-exposed humans. And when you look at the studies

that Dr. Smith published, where he specifically looked for the cytogenetic changes that you would associate with that in the bone marrow, they're not there.

Q. Doctor, are you familiar with this paper by Dr. Whysner about the genotoxicity of benzene and its metabolites?

A. Yes. I haven't read it recently, but I read it when it first came out.

Q. And it is a review paper that discusses all of both the animal evidence and human cell culture evidence with respect to the genotoxicity of benzene and its metabolites, correct?

A. No.

Q. No?

A. It discussed the evidence that was available to Dr. Whysner when he published this in 2004.

Q. At the time it was published. I wasn't trying to suggest that he was --

A. Well, there's been a lot that's happened since then.

Q. And the conclusion of Dr. Whysner's paper says, "Analysis of genotoxicity test results can provide important insights into the mechanisms of neoplasia produced by chemicals. After consideration of all of the available genotoxicity data for benzene and its metabolites, including the results of direct tests for DNA adducts, support a mode of action that involves clastogenicity rather than mutagenicity secondary to DNA adduct formation. In addition, information involving studies in

humans as well as human-derived cells indicate that such a mode of action would be operative in humans."

And then going down further he says, "The genotoxic effects produced by benzene and its metabolites are most consistent with inhibition of topoisomerase II or ribonucleotide reductase inhibition. The chromosomal abnormalities in human leukemia produced therapeutically by topoisomerase II inhibiters also implicate this mechanism in benzene-induced leukemias."

Now, isn't it fair to say that, based on Dr. Whysner's statement, information involving studies in humans as well as human-derived cells indicate that such a mode of action would be operative in humans, it's a fair interpretation of that statement that Dr. Whysner has inferred from the available evidence that he had reviewed as of 2004 when he published this paper that, in fact, benzene's metabolites inhibit topoisomerase in human beings?

A. That is a hypothesis.

Q. I understand that you think it's a hypothesis. I'm asking you whether it's a fair interpretation of that sentence in Dr. Whysner's paper that he inferred that it's a probability.

A. I think he thinks that it can happen, and I think now there is actually a little data that would support that that happens, in contrast to his last sentence which I think he would retract if he had the opportunity, and that is that

chromosomal changes associated with topoisomerase II -- that would be 11q23 -- that Dr. Smith said we don't see it.

Q. We'll get into that in a second, Doctor.

But, in fact, Dr. Whysner's paper was published in a peer-reviewed journal, correct?

A. Yes.

Q. So an editor had, initially, the opportunity to review this paper, correct?

A. Yes.

Q. And peer reviewers had an opportunity to review this paper, correct?

A. Yes.

Q. And all of those people apparently believed there was sufficient information to support the inferences that Dr. Whysner suggests in his conclusion here, right?

A. Well, you can't go that far. I mean, I don't know what the reviewers said. I don't know what they wrote. I don't know what executive decisions the editor made.

Q. Are you familiar with the Agency for Toxic Substances and Disease Registry's "Toxicological Profile for Benzene," Doctor?

A. Yes.

Q. And that's the ATSDR, correct?

A. That's its acronym, yes.

Q. And the ATSDR is an agency of the United States government -- a subagency of the Department of Health and Human

Services, correct?
A. I think that's correct. They're a branch of the CDC.
Q. I'm going to show you an excerpt from this August 2007 "Toxicological Profile for Benzene." And the ATSDR creates toxicological profiles for a wide variety of chemicals, correct?
A. Yes.
Q. And when they create that toxicological profile there's a committee that's appointed to look at all of the evidence that relates to the toxicity, human and animal studies and cell-line studies and mechanistic studies relating to the toxic effects of that chemical, correct?
A. I would assume that's how it works.
Q. And then they, as a committee, write a report that describes all that data, correct?
A. Yes.
Q. And also, in some instances, at least, make inferences from that data, correct?
A. Occasionally they'll put some things in there that you might classify as an inference.
Q. Okay. This is a section of the Toxicological Profile on Benzene called "Mechanisms of Toxicity." And it says, "The database of information for benzene-induced hematoxic and leukemogenic effects has been reviewed extensively. It is generally believed that reactive hepatic metabolites of benzene

are transported to the major toxicity targets (bone marrow). Additional metabolism likely occurs in bone marrow. Phenolic metabolites" -- and it lists them -- "appear to play a major role in benzene toxicity.

"Smith (1996a, 1999b)" -- and that's talking about two papers by Dr. Martyn Smith?

A. Yes.

Q. -- "noted that the phenolic metabolites can be metabolized by bone marrow peroxidases, such as myeloperoxidase (MPO) to highly reactive semiquinone radicals and quinones that simulate the production of reactive oxygen species. These steps lead to damage to tubulin, histone proteins, topoisomerase II, other DNA-associated proteins, and DNA itself (clastogenic effects such as strand breakage, mitotic recombination, chromosome translocation and aneuploidy)."

Would you agree, Doctor, that this suggests that benzene metabolites cause, among other things, damage to topoisomerase II in human beings?

A. Do I agree that's what they think or is that what they wrote?

Q. Do you agree that that statement suggests that?

A. Yes.

Q. Okay. Now, part of your opinion -- and you described this at some length with Mr. Gray this morning -- is that even if benzene's metabolites do inhibit topoisomerase II, that's not

evidence that benzene causes APL because certain known topoisomerase inhibitors do not cause leukemia, correct? That's your view?

A. Yes. That just because you can inhibit topo II doesn't get you to leukemia.

Q. And at your deposition, Dr. Pyatt, you gave this -- one example of a topoisomerase inhibitor that does not cause leukemia, genistein, correct?

A. That the evidence doesn't support that? Yes.

Q. In fact, you said that there's no evidence that genistein is leukemogenic, right?

A. I think that's still true with regard to direct epidemiology.

Q. But that's what you said: There's no evidence that genistein causes leukemia, right?

A. Well, it depends on how you're going to define the word "evidence."

Q. Well, you were the one testifying, not me.

A. It says what I thought.

Q. Okay. In fact, you've looked now, and there are epidemiology studies that address the issue of whether genistein causes leukemia, are there not?

A. No.

Q. There are not? Oh. Have you seen this paper before, Doctor?

A. Yes.
Q. And Dr. Osheroff is an author that you have relied on for purposes of your opinions in this case, correct?
A. Yes.
Q. For the record, the title of the article is "Survey and Summary: The DNA Cleavage Reaction of Topoisomerase II: Wolf in Sheep's Clothing" by Deweese and Osheroff. It's Nucleic Acids Research, 2009, and it was published online 28 November, 2008.
It says, "Epidemiological studies indicate that the risk of developing these infant leukemias increase greater than threefold by maternal consumption of foods that are high in naturally occurring topoisomerase II poisons such as genistein or other bioflavonoids." That's what it says, right?
A. Yes.
Q. In fact, so Dr. Osheroff is saying that there are epidemiological studies establishing an association between, among other things, genistein and infant leukemia, right?
A. That's not what he's saying.
Q. Hmm.
A. "Epidemiology studies indicate that" -- move it back over -- "the risk of developing foods that are naturally high in topo poisons such as genistein and other bioflavonoids" -- and then look at the papers. Let's look at the ones he cites.
Q. We could do that. 111, and 123 to 126. 111 is Strick

2000, "Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia."

A. Wait. Let's talk about that one.

Q. All right.

A. I'm very familiar with that study. So what they did was they went in and saw at certain concentrations these various bioflavonoids and flavones and other things could inhibit the -- well, could cause the MLL gene -- translocations involving the MLL gene, which is thought to be important in infant leukemia. So that's not an epi study.

Q. Okay.

A. The next one was 124.

Q. 123 is Ross, 1994. That's an epi study, right?

A. The Ross paper was the one we discussed in some detail this morning.

Q. And it's an epidemiology study, correct?

A. A very preliminary one, yes. And they did --

Q. They found a statistically significant increase in infant leukemia associated with maternal consumption of foods containing genistein, correct?

A. They found a statistically significant increase in AML -- infant AML -- associated with fresh fruits and vegetables. Everything else is hypothetical.

Q. Are you familiar with this paper, Doctor?

A. Are we finished with the other one?

Q. Do you want to go on?
A. I think that was it.
Q. Are you familiar with this paper, Doctor, "Review: Dietary Topoisomerase II Poisons: Contribution of Soy Products to Infant Leukemia"?
A. Yes.
Q. It's by Hengstler, H-E-N-G-S-T-L-E-R, published in 2002 in the EXCLI Journal.
A. I've read that paper.
Q. And the conclusion of that paper is, "In conclusion, strong evidence has been presented that dietary topoisomerase II poisons may contribute to infant leukemia."
So at least those authors believe that not only is there evidence, there is strong evidence for the proposition, correct?
A. You kind of lowered your voice on the most important word in there, that "may."
Q. Okay. Doctor, you talked about 11q23. Isn't it true that Dr. Smith's opinion is that benzene is causing -- or benzene's metabolites are causing a different kind of topoisomerase inhibition as opposed to poisoning that results in translocations at 15;17, which is different from the 11q23 mechanism?
A. He doesn't have a choice. He has to make that decision because the 11q23 is not elevated. So there's really -- if

it's acting as a topoisomerase II -- if it's causing leukemia by way of topoisomerase II inhibition, it is apparently acting through some way different than the typical topo II poison such as etoposide which cause the 11q23 the majority of time.

Q. Okay. You went over the Chang paper this morning in connection with 15;17 translocations, correct?

A. Yes.

Q. And this is the Chang paper that you discussed in your direct testimony?

A. Correct.

Q. There are other papers discussed in the Chang paper that show different results, correct?

A. Yes.

Q. The author says, "However, Takatsuki, et al, examined PML" -- and that's promyelocytic leukemia gene, correct? PML stands for -- well, promyelocytic leukemia gene.

A. I'm sorry. I'm reading. PML's promyelocytic leukemia and RAR-alpha receptor.

Q. -- "RARa in hematopoietic colonies in five patients with APL by reverse-transcription PCR and found the fusion transcripts in both granuloid/macrophage and erythroid colonies"?

A. That's correct.

Q. And that's consistent with --

A. Well, wait a minute. Go back to that. So what he says is

that maybe it's happening in an earlier cell or maybe there was contamination for the erythrocytes being in with the other forms of cells. He doesn't know why that's there.

Q. Right. And that's consistent with the damage or the -- being caused at this lineage or earlier, correct?

A. No, not earlier. But, yes, it would move it back to the common myeloid precursor cell. It wouldn't move it up any further because then you're going to have to start looking at the lymphoid cells.

Q. All right. And you just pointed out to me that there's alternative explanation for that. There's also an alternative explanation for the author's findings that there was no 15;17 translocation in the erythrocytes, correct?

A. Yes.

Q. And they discuss that. And their alternative explanation is, "Alternatively, it may reflect a blockage of differentiation for primitive precursor cells harboring translocation 15;17 toward the erythroid and lymphoid maturation pathway."

So what they're saying is that the translocation may be occurring up here but there's something blocking it from differentiating it as it's going down the line, correct?

A. Right. That is what they're saying, that you cannot rule that out as a possibility.

MR. JENSEN: Pass the witness.

MR. GRAY: Your Honor, may I inquire of counsel, are the textbooks that he relied on, the chapter by Goldstein and Kipen and the chapter by Kipen and Wartenberg -- were those the two?

MR. JENSEN: I'm sorry?

MR. GRAY: Were those the two chapters you relied on?

MR. JENSEN: Yes.

MR. GRAY: Can I ask for a copy of the Goldstein chapter, please?

MR. STEWART: It's in this binder.

THE WITNESS: He says you have it.

MR. GRAY: I'll go ahead and begin while counsel's -- you've got it there.

REDIRECT EXAMINATION

BY MR. GRAY:

Q. Dr. Pyatt, it's interesting, you were here for Dr. Smith's testimony. We didn't hear Dr. Smith testifying about these textbooks, did we? Do you recall hearing that?

A. I didn't, no.

Q. And that was Tuesday. It's Friday, at the end of the day, and we hear the first of these textbooks.

I'm going to ask you to read some language here on the point -- this is Table 29.1, which is what counsel suggests it indicates a textbook found that APL was caused by benzene, right?

A. Yes.
Q. Okay. And in the text just above there, there's a footnote reference for Table 29-1. That's Footnote 7, correct?
A. Yes.
Q. And I think in your testimony when you were answering these questions you said it would be nice to look at the references to see what this author was using as support for this statement?
A. Yes.
Q. Okay. Let's look at Footnote 7. In Footnote 7 Dr. Goldstein is referring to a paper that Dr. Goldstein wrote in 1983; is that correct?
A. I've seen that. That's a review paper.
Q. Okay. So luckily we brought that. And when you flip to the review paper by Professor Goldstein, it has a table where he says essentially the same thing, that acute myelogenous leukemia is caused by benzene; do you see that?
A. Yes.
Q. And then Dr. Goldstein, the good researcher who he is, sites Reference 18 as support for this paper. Let's look at Reference 18. And there's Dr. Goldstein citing Dr. Goldstein again, 1977. We brought that one, too. Would you like to see that paper?
A. Please.
Q. I apologize for using my finger here, but it says, "In

discussing the types of AML which can be caused by benzene" -- it says -- "and acute promyelocytic leukemia" -- et cetera, et cetera, et cetera -- "have been rarely reported in association with benzene"; do you see that?

A. Yes.

Q. What reference does he cite for that statement?

A. I don't see one.

Q. He cites nothing, correct?

A. I would assume he was looking at the Askoy or the Vigliani studies because there isn't really anything else to be looking at prior to 1977, but I don't know.

Q. But those studies didn't say that benzene causes APL, do they?

A. No.

Q. So Goldstein writes a paper in 1977 where he suggests benzene might cause APL, true?

A. Yes.

Q. And then he writes a paper in 1983 that says benzene does cause AML, and he cites the '77 paper, true?

A. Yes.

Q. And then writes another chapter in his textbook later and he cites his '83 textbook, right?

A. Yes.

Q. Does Goldstein cite anything to support this statement that benzene causes APL other than his own previous statements?

A. Not that I saw based on what you saw me. But I haven't looked at the reference list for that chapter so I don't -- but not based on what you've shown, no.

Q. And certainly if Dr. Smith thought this chapter was persuasive, he could have testified about it on his direct exam?

A. I would think so, yes.

Q. Let's talk about the other chapter.

MR. JENSEN: It was in his reference...

BY MR. GRAY:

Q. And I believe this is the other book, "Textbook of Clinical Occupational and Environmental Medicine," correct?

A. Yes.

Q. Okay. And here, I think, is the table that you were asked to look at where it's discussing benzene. "Known: AML and variants." And there's three footnotes there, correct?

A. Correct.

Q. And that's what you said you would have liked to have seen, is what are these authors referring to, right?

A. Yes.

Q. So let's look at 7, 63 and 95. If you could help me remember those. Seven --

A. I'm listening.

Q. -- is a paper by Hayes. You're familiar with that one?

A. Yes.

Q. Now we're going to go to 63. There's our good friend Dr. Rinsky?
A. Yes.
Q. We had a lot of discussion about Rinsky's work, right? And 95, another paper by Rinsky?
A. Correct.
Q. Do any of those three papers say that benzene causes APL?
A. No.
Q. Okay. And we've discussed those pretty extensively.
MR. GRAY: What I would like to do is mark these articles I've just discussed for part of the record, and perhaps I can work it out with the clerk afterwards --
THE COURT: That's fine.
MR. GRAY: -- but I would certainly like these to be included for the Court to consider.
BY MR. GRAY:
Q. Briefly, the Whysner paper. As to the question of whether or not benzene causes leukemia due to topo II inhibition, isn't it true that Dr. Whysner cites your paper, page 116, and says, "Serious questions have been raised concerning the role of topoisomerase II inhibition in benzene-induced human leukemia and additional studies will be needed to provide validation of this mechanism." Did I read that correctly?
A. Yes.
Q. And I know you pointed this out, but just briefly, here in

the "Conclusion" language that counsel read, that last sentence is pretty important, isn't it?

A. Yes.

Q. Because in 2004, Zhang had not yet done the study that showed benzene does cause 11q23?

A. No.

Q. And is that why you suggested he wrote that paper based upon the information he had at the time?

A. Yes.

Q. Okay. With respect to the discussion of cell of origin, the scientist who had specifically looked at cell of origin for APL since -- well, all of the studies we've looked at from '95 forward -- would you say that the researchers who had specifically looked at cell of origin for APL, that the bulk of that literature indicates that it is a different cell of origin from other subtypes of AML?

A. I would. I haven't seen any research specifically address APL without discussing that it is likely occurring at a committed precursor level. When they talk about AML, then maybe it's up here or maybe it's up there. But when they break it out and talk about APL, yes, that's true.

Q. And you will find statements in the literature where researchers are talking about AML generally, and they make very broad statements about AML, correct?

A. That's true.

Q. And it would be important to look at that particular piece of literature in determining whether that author considered these APL-specific studies in deciding whether or not the author is making a specific conclusion about APL; is that fair?
A. I think that's exactly right, yes.
MR. GRAY: Your Honor, if I can have your indulgence. I have one final question.
Your Honor, actually, if I stop now, we may finish before the break, so I'll pass the witness.
MR. JENSEN: One follow-up area, your Honor.

RECROSS-EXAMINATION

BY MR. JENSEN:
Q. Dr. Pyatt, you just testified that you were aware of no literature that you'd seen regarding the 15;17 translocation or APL occurring at anything other than a committed cell level over the last 15 years. Is that what you just said?
A. I mean, I think all of them raise the possibility that could happen someplace else, but, yes.
Q. Well, in fact, we just went over on your cross-examination how the Chang paper discusses the Takatsuki article or study, and they found out, in fact, how the 15;17 translocation was occurring at a progenitor stem cell -- excuse me, progenitor cell level that can produce all of the forms of AML, right?
A. Well, I think what I said was that it was happening at a committed precursor. And the CMP that you're referring, to

that is a committed precursor.

Q. Okay. So that's a precursor that can generate all of the cell lines for all of the subtypes of AML, right?

A. Conceivably, yes.

MR. JENSEN: All right. That's it.

MR. STEWART: He didn't mean to stand up and interrupt Mr. Gray beforehand. What I was attempting to make sure the Court knew was that the Levy-Wegman article is Number 43 in the binder of materials, and it's under the category of things that Dr. Smith relied on.

MR. GRAY: And, your Honor, I certainly wasn't suggesting it hadn't been disclosed; I was just questioning why Dr. Smith hadn't been questioned on it.

MR. STEWART: There were 62 things in the binder. I didn't want to do them all. In any event, I wanted the Court to know it was in the binder materials.

THE COURT: Dr. Pyatt may be excused, right?

(Laughter.)

MR. STEWART: Thank you, your Honor.

THE COURT: We'll re-assemble at two o'clock.

MR. WEATHERS: Your Honor, a brief moment. I find that I have to catch a plane that will conflict with that. If I don't catch that, it's hard to get home tonight.

THE COURT: You're not staying for the Red Sox-Yankees game?

MR. WEATHERS: The Boston guys didn't get me tickets.

But in any event, your Honor, I apologize that I have to leave early and ask to be excused.

THE COURT: I understand.

MR. GRAY: And, your Honor, I'm checking flights myself.

THE COURT: All right.

MR. WEATHERS: We leave it in Mr. Leghorn's good hands.

THE CLERK: We'll be in recess. Court is in recess.

(There is a recess in the proceedings from 12:58 p.m. to 2 p.m.)

THE CLERK: All rise.

Continuation of the Milward Daubert hearing.

Please be seated.

THE COURT: Okay.

MR. JENSEN: Good afternoon, your Honor. I believe we've designated one hour, so 30 minutes each, and --

THE COURT: Or less.

(Laughter.)

MR. JENSEN: Or less. I agree. I intend to reserve eight minutes for rebuttal.

May it please the Court, I know the Court's read the briefs. And the briefs open by saying the Court should keep the eyes on the forest and not get blinded by the trees. And

with all the evidence that we've heard the human temptation is to do that. So I want to start by reminding the Court of what the forest is.

First, of all, as a matter of law, this Court has a very limited role as the gatekeeper of scientific evidence; secondly, the Court should keep in mind, with respect to the science, that the methodology is where the focus needs to be, and the methodology at issue here which no one has contested is the weight-of-the-evidence method reviewing the available scientific evidence, and that method, which also no one else has contested, clearly and necessarily calls for the extensive application of scientific judgment at several places throughout the process. And finally, as I just said, they failed to offer any challenge to that method.

According to the McGovern versus Brigham and Women's Hospital, which is a 2008 district court stemming from this court, the role of this Court as a gatekeeper can be distilled into three questions: First of all, is this junk science? I'm talking from a PowerPoint that no one else has seen.

THE COURT: You are, hmm?

MR. JENSEN: The first question, according to the McGovern court, 2008 District of Massachusetts case: Is this junk science? I don't think the defendants take any position that the epidemiological literature, the toxicology literature, the mechanistic literature, that any of that is junk science,

nor do I think they take the position that Martyn Smith is a junk scientist. And if they did it would be frivolous. What they do is that this is a junk opinion, and that is what this Court has to decide.

What is a junk opinion according to the law? Some light has been shed on that by some comments made in the introduction to the Federal Judicial Center's Reference Manual on Scientific Evidence. That introduction was written by Justice Stephen Breyer. He said, "Consider the remark made by the physicist Wolfgang Pauli. After a colleague asked whether a certain scientific paper was wrong, Pauli replied, 'That paper isn't even good enough to be wrong!' Our objective is to avoid legal decisions that reflect that paper's so-called science." That's what we're aiming at.

More specifically, the First Circuit has made clear that "Daubert neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance." "Once the district court finds that the expert's methodology is reliable, the expert is allowed to testify as to the inferences and conclusions he draws from it."

In other words, this Court's role is not to determine which side is correct and whose conclusion is right. You don't have to decide whether benzene can cause APL. All you have to decide is whether Martyn Smith exercised a reliable, sound scientific methodology when he reached his conclusion.

Credibility is solely for the jury, and when experts disagree based on differences in application of scientific judgment, that disagreement has to be resolved by an assessment of credibility, and that role constitutionally belongs to the jury, and the jury alone. "Trial courts should not arrogate the jury's role in evaluating the 'evidence and the credibility of expert witnesses' by 'simply choosing sides in the battle of the experts.'"

Now, what did Dr. Smith do in this case? Methodologically, he applied the well-established method for assessing causation, the weight-of-the-evidence method that no one in this courtroom has suggested is the -- is an incorrect method. Dr. Cranor referred to it from the philosophical perspective as inference to the best explanation. That same method is used by many government and other agencies that are assigned the role of assessing whether certain chemicals cause cancer, including IARC, the National Toxicology Program, the EPA.

And I think this quote from the American Law Institute's Restatement (Third) of Torts is significant. "Scientists report that an evaluation of data and scientific evidence to determine whether an inference of causation is appropriate requires judgment and interpretation. Scientists are subject to their own value judgment and preexisting biases that may affect their view of a body of evidence. There are

instances in which, although one scientist or group of scientists comes to one conclusion about factual causation, they recognize that another group that comes to a contrary conclusion might still be reasonable. Judgments about causation may also be affected by the comparative costs of errors as when caution counsels in favor of declaring an uncertain agent toxic because the potential harm it may cause, if toxic, is so much greater than the benefit foregone if it were permitted to be introduced. Courts, thus, should be cautious about adopting specific scientific principles taken out of context to formulate bright-line legal rules or conclude that reasonable minds cannot differ about factual causation."

The point of this, your Honor, is this -- or one of the points: Defendants have strenuously argued in their briefs, and it's apparent from their expert testimony, that their primary position as a matter of law in this case is that there must be statistically significant formal epidemiological studies that show an association between benzene and APL specifically in order for Martyn Smith to reach a reliable admissible opinion under Daubert. And that's wrong as a matter of law and it's wrong as a matter of science.

On to the role of scientific judgment. Dr. Cranor discussed the Rudén article which gives an example of reasonable scientists coming to reasonable disagreement, all having reviewed exactly the same evidence. Seven agencies were

assigned the task of assessing the same body of epidemiology studies on TCE, including IARC, the ACGIH and European agencies. None of them could agree about anything except -- well, four of them agreed the data was negative; the three that said it was positive were talking about different studies and different types of cancer in order to establish a positive association; thus, there is inevitably going to be scientific disagreement with the application opposite views.

I've already discussed that epidemiology is not a sine qua non. I think it's important to remind the Court of what the NTP listing criteria for "reasonably anticipated to be a human carcinogen" includes. This is the third of three possibilities that can satisfy that criteria as listed by the NTP. You can be satisfied by "less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well-defined structurally related class of substances whose members are listed in a previous report as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating that it would likely cause cancer in humans." That's the kind of information that Dr. Smith was relying on, in part, in his opinions in this case.

I remind the Court to look at Exhibit 6 to the plaintiffs' opening brief which is an article by a scientist

with the National Institute of Health discussing how epidemiology is not required. Dr. Smith testified to this; Dr. Cranor testified to this; IARC and NTP establish it. That's what scientists do. They can reach general causation opinions without necessarily having positive statistically significant epidemiology findings.

THE COURT: Let me just ask you this: Isn't the point of epidemiological studies that the phenomenon actually has been observed as opposed to theorizing about whether it might be observed? Isn't that a role for epidem- -- in other words, the historical or empirical rather than, for lack of a better word, theoretical or --

MR. JENSEN: Well, I mean, I think a lot of toxicologists would fence with you, your Honor, about whether a mechanistic study provides merely a theory about what's going on in the body. A lot of toxicologists would say, look, once we've done a test, the laboratory test that's controlled that establishes that this effect occurs, then it's not a theoretical; it is at the very least probable. You have to make a few inferences about going from the laboratory setting to elsewhere. But it's not merely theoretical.

Now, is epidemiology about observation in humans? Clearly it is. It has its own set of limitations just as toxicology has its. But they're both -- the important point for this Court as a matter of law is that scientists can

integrate those kinds of evidence, and the scientists who assess this kind of very issue, whether a chemical causes cancer, do not, as a sine qua non, have to have epidemiology to reach a more-likely-than-not conclusion.

Now, is it certain? No. There's going to be uncertainty associated with it. But a more-probable-than-not conclusion like reasonably anticipated to be a carcinogen or a probable carcinogen, which is the way IARC puts it, does not require epidemiology as a sine qua non.

In fact, Dr. Bennett gave us a really good example of having a finding of causation without the requirement of epidemiology. He said, quote, "We know that we can cause APL in patients whom we administer chemotherapy, and that's what we refer to as secondary AML, and there are well-described multiple case reports and series of chemotherapy compounds that interfere." And you heard this discussion, blah, blah, blah.

He was talking about chemotherapeutic agents causing APL and secondary AML from case reports. But he said, "We know that we can cause APL, but the case reports indicate" --

That's not formal epidemiology; in fact, that's less scientific than toxicology studies in a controlled laboratory experiment.

Daubert doesn't require it. There's a whole series of cases that we've already cited to the Court.

Dr. Smith's four lines of evidence, the Court will

recall, are the epidemiology of benzene and AML generally; the common cell of origin for all AML subtypes -- or his opinion that there is a common cell of origin for all AML subtypes; his opinion that the inhibition of topoisomerase II by benzene's metabolites is a probable cause of APL; and what information he can glean out of the few epidemiology studies that have any APL-specific information with regard to benzene-exposed populations.

As to the epidemiology of benzene and AML, it's undisputed by all experts that benzene causes AML. It's undisputed that the studies satisfy the Bradford Hill considerations; the defendants have pointed to no published literature that benzene causes some but not all types of AML; and the defendants make no argument regarding Dr. Smith's method for analyzing this literature. He used a weight-of-the-evidence review just as is done by everyone else.

As to the common origin of AMLs. Dr. Smith's opinion is that all subtypes of AML arise from the same progenitor or stem cell. Now, clearly Dr. Bennett and Dr. Pyatt have testified over the last two days that they disagree with that. They both, however, have testified that reasonable minds and reasonable scientists can and do differ on that very issue.

On the second piece, benzene causes chromosomal damage at the progenitor cell level before the cells have completely differentiated, at the level of what we've been describing as

the CMP, where all AMLs can descend from, benzene is causing that damage. Undisputed.

Shown in this study, Lan, et al, of course one of Dr. Smith's studies, in which benzene is attacking the CFU-GEMM cell, one of the progenitor cells from which all AMLs descend. You can see the CFU-GEMM there.

As I said, Dr. Bennett and Dr. Pyatt agree that reasonable scientists disagree. Dr. Pyatt testified that hematopoietic progenitor cells are a target tissue for benzene toxicity, and neither Dr. Pyatt nor Dr. Bennett challenged Dr. Smith's methods for reviewing the literature and analyzing this issue. They weren't challenging his method; they were challenging his conclusion.

Your Honor, if we were here to decide whether benzene causes APL or to decide this sub-issue of whether all AMLs have a common origin, that would be a dog fight. What's not a dog fight is what the Daubert requirements limit your role to, which is did Dr. Smith reach an inference based on data that was available using the proper methods. There's really no contest about that.

THE COURT: If -- let's make an assumption.

MR. JENSEN: Sure.

THE COURT: If the evidence were to be such that it appeared that Dr. Smith's opinion could properly be classified as an hypothesis, would that be sufficient to permit a jury to

conclude that it was more than that?

MR. JENSEN: Well, your Honor, it depends on what you mean by a "hypothesis." There is data from which reasonable scientists -- not just Dr. Smith, but reasonable scientists -- the ATSDR, John Whysner -- others are inferring that probably this is what's happening. So, you know, if you're describing a hypothesis as something that hasn't been certainly proved by either, you know, 95 percent statistical certainty observation or by some other clinically verified experiment, then, yeah, I mean, so long as someone has data from which they can make an inference that supports a more-likely-than-not explanation, then, yes, it is admissible.

THE COURT: Well, I guess my -- let me ask it a different way. You might have a case where an expert for the plaintiff says A causes B, and an expert for the defendant says A does not cause B.

MR. JENSEN: Right.

THE COURT: And the jury would then, I guess, evaluate the presentations and decide whether the plaintiff was more persuasive than alternate explanations including, perhaps, the defendants', although the burden would be on the plaintiff.

What I was trying to isolate is the case where it's fairly understood the plaintiffs' supporting opinion was that A very well might cause B, and the response was there's not sufficient evidence that it does. In that case would the

statement from the Ruiz-Troche case, that it's up to the jury to evaluate the provenance be applicable, or is that a case where the Daubert gate becomes important?

MR. JENSEN: Well, your Honor, if the inference that the expert at issue has made, as far as that expert is willing to go from the data is to say that it might happen, I think that that may well be an occasion that --

THE COURT: Well, there could be two occasions -- two expressions of that, I suppose, whether explicitly that's the opinion --

MR. JENSEN: Uh-huh.

THE COURT: -- or alternately, whether the opinion, although not explicitly limited to a possibility, or a plausibility, is fairly understood that way rather than as an assertion at a higher level of confidence, I guess.

MR. JENSEN: Well, I don't know with respect to the second position unless I had more information. I can tell you this: Dr. Smith's opinion is that it is not merely plausible that benzene causes APL through topoisomerase inhibition; it is probable. It is not merely plausible that all AMLs start from a common cell of origin, but it is probable. And that is his opinion.

And therefore -- and there is data from which reasonable scientists -- not just Martyn Smith but others -- can and do make those same kinds of inferences. And, in fact,

defendants' witnesses, to a large extent, acknowledge that very fact. And so in this case you don't have to reach the issue that you just asked me about.

THE COURT: Let me ask it in even a different way. Referring to the Rudén article where there are three who say one thing -- or they actually say three things, but you classified them as one thing -- and then you have four who say something else.

If that were all presented to the jury, would the jury be able to rationally decide among them?

MR. JENSEN: Well, it is the jury's responsibility to do that. It is the constitutional delegation --

THE COURT: What would be the tool that the jury would use?

MR. JENSEN: All the information and assessment of the credibility of the various experts who would be coming in and explaining why they reached the inferences they reached. It's the jury's role -- it's clearly a scientific judgment issue. And once you get to a decision tree -- a point in the decision tree where resolution of that decision requires application of what is subjective scientific judgment, whose judgment is better than the -- which person's judgment is better than the other is the jury's role to decide and not yours.

THE COURT: So the jury could decide because four say one thing and three say the other, they would go with the four?

That would be a way of resolving it.

MR. JENSEN: Well, they could decide on whatever basis they assess the credibility of the witnesses.

THE COURT: And we would never know. It's a black box.

MR. JENSEN: We would never know. Sometimes we interview them, but we can't know. And that's their job. That's the way our Constitution works. It's their position to do that, whether it's scientific evidence or any other kind of evidence.

THE COURT: All right.

MR. JENSEN: There's an additional line of evidence by analogy that we didn't describe as being one of the four prongs of Dr. Smith's opinion, but it's nonetheless of some significance here, which is the evidence that Dr. Smith mentioned that benzene is capable of causing all subtypes of AML as drawn from the analogy to radiation. Benzene is considered radiomimetic in that it acts in a very similar way to ionizing radiation which is known to cause all the different kinds of leukemia including AML -- excuse me -- including APL.

Now, on to topoisomerase inhibition, quickly. Dr. Smith's opinion I think the Court is well familiar with. As to the defendants -- well, first of all, the ATSDR I went over with Dr. Pyatt have established that benzene does, in fact, inhibit topoisomerase II, and Dr. Pyatt admitted that this

statement in the ATSDR should fairly be read to say -- the ATSDR is saying it inhibits topoisomerase II not just in a cell culture but in human beings. That's what they think. And Dr. Whysner thinks the same thing. In fact, he goes farther than that to say not only is it likely inhibiting topoisomerase in humans, but that inhibition is, in fact, causing leukemia.

It is well accepted that topoisomerase II inhibitors induce APL. Not only is it in the literature, but Dr. Bennett testified about it.

There is no methodology critique -- again, this is about a battle of the experts on a conclusion. They've reached different inferences from reviewing the same body of data. The methods that they've applied on each side of the aisle were exactly the same. They looked at the same literature; they made inferences from it. Some thought it supported one inference; some thought it supported the other. That is a scientific judgment issue that is a credibility role for the jury.

And now let's take a look at the trees, which is what Mr. Leghorn's going to spend all his time talking about.

THE COURT: You're going to run into your eight minutes. Do it quickly.

MR. JENSEN: All right. Dr. Smith -- and this is important -- said that he didn't need anything -- any of the data from the so-called APL-specific epi studies to reach his

opinion. There's only one study out there that sought to measure association by subtypes. That's the Acta case-control study, the Chinese case-control study not to be confused with the big Hayes-Travis NCI study, which is a cohort study. No cohort study has been designed to test this out. And the Acta study, in fact, finds an elevated association, although it wasn't statistically significant.

The Mele study we've heard a lot about. The Court knows what that's about. It does find a positive association with benzene-exposed workers. The Travis study -- and I'm going to skip over Travis for now because I want to go to Golomb, because I know Dr. -- excuse me, Mr. Leghorn -- I've elevated him -- is going to talk a lot about Dr. Smith's opinion about the Golomb paper.

And here's what happened: He made a mistake. He really did. He reached his opinion originally that benzene can cause APL by the mid-'90s. So my point of this slide is that the mistake that he made, which I'll explain in just a moment but I think the Court is aware of it -- the mistake he made had no impact on his opinion. He'd already reached his opinion by the mid-1990s. The Zhang paper, that had contradictory criteria that Mr. Leghorn's going to talk about, was published many years later. Obviously, whether he determined that the seven people in the Golomb paper who were exposed to chemical solvents and metals are best characterized as having possible

benzene exposure or probable benzene exposure is not a make-or-break determinant of the overall opinion.

And, you know, Dr. Smith agrees that he shouldn't be applying a different set of criteria in his research and his litigation opinions. He'd forgotten what he'd said in the Zhang paper and he made a mistake. But that mistake has very little bearing in the scope of the forest. One study he relied on had more than 60.

I reserve the rest of my time, your Honor.

THE COURT: Okay. Thank you.

Mr. Leghorn?

MR. LEGHORN: Thank you. Your Honor. This is a Daubert --

THE COURT: Use the podium.

MR. LEGHORN: I was going to use the chart. Then I can't use the chart.

THE COURT: Okay. But you have to be near a microphone.

MR. LEGHORN: Okay. That's fine.

This is a Daubert hearing, and the issue is: Is the methodology that Dr. Smith used -- does it meet the standard of medicine, science, epidemiology to draw the conclusion that APL can be caused by benzene or does benzene cause APL? And the question has been explored in different ways.

One approach that we've heard here and heard from Dr.

Smith was that -- and the defense witnesses agreed. Benzene at certain levels of exposure can cause certain forms of AML. And Dr. Smith admits that in most cases those have abnormalities at the fifth and seventh chromosomes. The other part of his argument is since APL is a form of AML and benzene causes AML, therefore benzene causes APL. That's the classical logical fallacy of the undistributed middle. It's up to -- in that argument, what Dr. Smith has to do, through his methodology, is show that APL is the same as AML.

It's not, by his own admission. APL, according to Dr. Smith, has an abnormality at Chromosome 17. Dr. Bennett, a world-renowned hematopathologist: APL is different. It's not the same. It has certain marks. It has a certain signature. Others, as you look at the Eastmond study, have other marks. The M6s have a mark at the 11q23, I believe -- or the M4s and M5s have that -- and the M1s and the 2s at the 5s and the 7s. So the question is, that's one of the things that they have to show in the methodology to get there to show that APL and AML are the same.

The evidence to do that doesn't come together. As Dr. Pyatt talked about, it is a straight line. What is the straight line that gets us to that point? Science is based upon objective observations from which conclusions are drawn. At the end of the day there's no objective data, by Dr. Smith's own admission, that you see the t(15;17) translocation in the

benzene-exposed that is -- that he could relate to benzene exposure. Remember, he also says on that straight line that the 15;17 translocation occurs generally in the population, and only one out of a thousand of those become APL; admits that it is -- benzene exposure can only -- is a necessary, but not sufficient, cause.

We never heard from Dr. Smith -- and it's plaintiffs' burden to demonstrate his methodology of what about the benzene exposure triggers anything that becomes a sufficient cause of APL. And one of the things that you always have to look at in the methodology of -- to draw the ultimate conclusion that APL -- that benzene can cause APL is based on a variety of factors, as Hill said. And if you do look at the scientific manual when it comes to epidemiology or -- and general causation -- I think, unfortunately, the human frailty, that's the best system that we have of noticing association, there are ways of doing that.

And it's only when you have that association that you begin the rest of those inquiries. And as Dr. Garabrant and Dr. Smith in their own ways -- Dr. Smith in his own way concedes, a case-control study can yield good information. It's not always the cohort study. In fact, his manipulation of the Golomb data mistake was treated as a case-control study. And sometimes if someone has a hypothesis -- and in the Acta, or the study that is written in Chinese and translated, those

researchers looked at benzene in relation to a number of subtypes of AML. They did not find a statistically significant association between benzene exposure and APL, the M3 variety.

They looked at 171 cases of APL and 342 controls, I believe. Dr. Smith, in coming to his conclusion, looked at two cases in Mele; four cases in the Travis study; and three, four or five cases in Golomb. Two of those studies didn't measure benzene exposure. He didn't do, when he made his calculations, any analysis to see whether those occurred by chance. And as Dr. Garabrant's presentation showed, he did -- Dr. Smith's Golomb calculation correcting for the inexplicitly missing case in the calculation. And accepting Dr. Smith's throwing out of one, it still comes out to a result that was more likely than not the result of chance.

On the stand, under oath, he said he applied different criteria. It was -- your Honor, you talked about the jury being a black box. The expert and the methodology cannot be a black box either. For you to evaluate, you have to be able to understand the steps that were taken. You have to understand the evidence, or the data, that was reviewed. The defendants' presentation was to let you understand that data.

It's interesting, Dr. Smith said he formed his opinion that APL was caused by benzene in 1995. In light of what data? Never heard that. He doesn't account for the contrary data to a number of other things that he built into his opinion. One

tutorial study was in 1995. If he believed as part of that opinion in 1995 about the stem cell approach, he didn't account for the contrary data that occurs afterwards.

If you believed Dr. Cranor that you have to, in offering your opinion in court, consider all the data and offer an opinion, the witness -- the expert witness has to explain to your Honor how he came to that conclusion looking at all of the data.

Turhan says a single pluripotent stem cell approach doesn't work. Subsequent data, Chang and others, say it doesn't work. We don't know if or how Dr. Smith accounted for it. We don't know, other than simply dismissing it by paying no attention to the study behind the curtain, why or how he did not consider the lack of an epidemiological finding in the Acta Chinese study was evidence that there was no association. You don't have evidence of one, and when there was an observation, not statistically significant, dismiss it. That's one of the problems in demonstrating the methodology here.

And certainly as Dr. Pyatt testified, much has been learned in the last few years about hematopoietic stem cells, where the insult might have occurred, how it might have occurred. And so when you look at it, we don't have that basic epidemiological association, and plaintiffs rely entirely on this, "We have a mechanistic approach," but it is a mechanistic approach that has missing pieces, and where you have to put

together disparate and unconnected information to arrive at a conclusion. It is not a simple A to B to C to D to E to F. One's missing. You've got to go up to C+, to look there with regard to other chemicals, with no demonstration that some of the chemotherapy agents act in the same way.

Dr. Smith admits on the stand for -- telling us about unpublished papers for the first time that what he told us earlier about benzene and bringing about the 11q23, that doesn't occur. So even he, in that regard, is accepting some of the substance, but he doesn't tell us how he rules out or rules in anything since he supposedly formed this opinion in the mid-1990s, and offers no explanation in his report which cites many studies since that date, what the basis of that original opinion is and how it might have evolved today based upon the current evidence.

So I think when you look at it, the methodology here was one of saying, "I can contrive by using some data from Golomb, by doing -- creating some cases of additional APL using the Travis data, that there's some kind of statistics here -- whether it's significant or not, it doesn't matter to me -- and I've got an association now, which is really the beginning of the scientific inquiry as to whether there is truly cause -- and offering nothing more."

The real key here is, your Honor, that as Dr. Garabrant and Dr. Pyatt and Dr. Bennett, Dr. Smith's opinion

that benzene can cause the t(15;17) in a mechanistic way is not supported, and, in fact, he says it is not been observed, although he hopes it will be in the future. That's not today. And that's not for sure. The hypothesis is that "With better technique we will confirm my hypothesis." And that's key for his mechanistic model. And it's just not there. There's no -- there is no statistically significant epidemiology. There's no contrary epidemiology in a large, powerful study. And Dr. Garabrant indicated that that study had power to find an association if it existed.

Dr. Smith says it's impossible to do this. "Did you do any calculations to determine that?" "No." There are methods and techniques, as Dr. Garabrant said, to do it. There are ways to do it. The methodology is flawed here, is not accepted within the community, and much remains unexplained.

So in conclusion, your Honor, because there is a lot here, but not much to support the admission under the Daubert standard of Dr. Smith's opinion.

Thank you.

THE COURT: Let me ask you, I read something from the Ruiz-Troche case, where the Court said, "Daubert does not require the party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct. Daubert neither requires nor empowers trial courts to determine which of several competing

scientific theories has the best provenance, demands only that the proponent of the evidence show that the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion."

So I think that's -- plaintiffs' argument is that judgment about the provenance, the ultimate worth of the arguments, I believe, are conflicting opinions is one committed to the jury. Why doesn't that language from Ruiz-Troche point in that direction?

MR. LEGHORN: Because, your Honor, we're focusing on the methodology here. If you're going to say that we have a sufficiently defined explanation of biological plausibility, you have to have that with the two end points: one, exposure; and, two, an observed t(15;17) because of that.

Here, while there are problems in the middle, there's no observation of that outcome even by Dr. Smith's admission. He's looked for it. He can't find it. He hopes to find it in the future. To say one, two, three, four, and thereby you get there -- he says, "We've looked. We don't see it."

So to draw the conclusion from the lack of evidence is not methodologically appropriate in a scientific arena. You have to have some objective data. That one is not there. By his own admission. The McHale 2008 paper says it's inconclusive. Those aren't my words; those were his. So, you know, he's missing the key end point on the biological

plausibility, even if you accept the middle.

And I think, your Honor, to let that go to the jury, ask them to make that decision which he cannot and has not observed, it doesn't work in that respect. And I think that that's different from saying, based upon these observations which all flow together from A to F, from the exposure to the end point, we've connected the chain, is different from saying we've connected the chain -- and I predict, although I've tried and haven't seen it -- I predict we'll see it. It's different. And I think that's the flaw in the methodology of allowing the biological plausibility theory here.

Thank you, your Honor.

THE COURT: Mr. Jensen?

MR. JENSEN: It's not an issue of -- certainly it's an issue of probability. It's not speculation if he says it's probable from the data that I can infer that benzene, or its metabolites, cause the 15;17 translocation. And by the way, he's the most qualified scientist in the world to answer that question because he's the only one that ever looked. He's published more on chromosomal translocations and benzene metabolites than anyone in the world.

And it's not merely that he says, "Oh, I hope that it will happen." He hopes that it will happen based on data. What's the data? A, that he knows that the epidemiology establishes conclusively that benzene causes AML as a group;

and, B, that the weight-of-the-evidence review that he's done of mechanisms and the pathological genesis of AMLs as a group is that they all start at the same spot, and that benzene causes damage at that spot.

From that, together with the fact that benzene inhibits topoisomerase, and other topoisomerase inhibitors have, in fact, been demonstrated to cause the 15;17 translocation -- they want to talk about 11q23. 11q23 is not APL. 15;17 is APL. 15;17, according to Dr. Smith's unrebutted testimony, is caused by a different topoisomerase mechanism than the 11q23. 11q23 is a red herring.

Let's talk about what the evidence is, and it's evidence from which reasonable scientists can draw the inference that more likely than not benzene and its metabolites cause APL. That's what Dr. Smith has done based on reliable methods of reviewing the evidence of which there's no contest about. The only methodological contest that Mr. Leghorn wants to talk about is what Dr. Garabrant wants to talk about in the review of the data -- the little snippets of data that Dr. Smith was able to glean that are APL-specific out of a few epidemiological studies or case series.

That was the fourth leg of a stool that stands quite well on three legs, as Dr. Smith said, number one. Number two, Dr. Garabrant's opinions about methodology on formal epidemiological studies misses the point. Dr. Smith wasn't

attempting or purporting to conduct formal epidemiological studies; all he was trying to do was see if what little data he could glean out of Travis and Golomb, out of the other paper, the Yang paper, are supportive or not supportive of the hypothesis that he says is probable and established by the other three lines of evidence already.

He didn't even need that fourth line of evidence. He checked it and he found it was consistent with the other three. Dr. Garabrant didn't like his opinions and didn't like his methods because he said they weren't formal epidemiology. Well, Dr. Smith made no claim that they were.

Mr. Leghorn contends that the Acta study is affirmative evidence against benzene causes APL, and that's ridiculous and unscientific. Epidemiology can never prove the null hypothesis. Multiple scientists testified to that here. Not only that, it's not even a negative study; it's a positive study. There's a positive association in that study between benzene and APL. Now, it's not significantly significant. It's possible that chance accounts for that positive association. But to the extent it shows us anything, it shows us some evidence that there is an association.

Is that evidence enough in and of itself? Of course not. But that's not the primary basis for Dr. Smith's opinion. The primary basis for Dr. Smith's opinion were the first three prongs of his analysis. Benzene causes AML, well-established

fact; all AMLs probably originate from the same stem -- from the same cell; and topoisomerase -- benzene inhibits topoisomerase, and topoisomerase does cause APL.

Put all of that together, and Dr. Smith says those are the three major prongs of my opinion. All of those are probable. Reasonable scientists do not have any disagreement about prong one; and as to prong two and three, their experts agree that reasonable scientists can disagree about it. There's enough data there that you can make the inference that this probably is occurring the way that Dr. Smith suggests that it is.

If you can make that effort -- inference based upon the data -- and they have admitted that you can, and you apply the correct methodology, which they haven't even contested -- this is not a close question. We brought you one of the best benzene scientists in the world. The colloquy between Mr. Stewart and Dr. Bennett yesterday I thought was extraordinary. I don't know if the Court's ever heard anything about it before. One witness said, "I am not an expert in the causation of acute myeloid leukemia but the other expert is a really good expert on that." He didn't say "really good"; he said he's an expert.

We brought you the guy. It's not a junk opinion. There's no basis for this Court to override the scientific judgment credibility battle that's going on here. We may have

a dog fight with the jury; this is not a close question for the Court.

THE COURT: All right.

MR. LEGHORN: One comment on that. With regard to the 11q23, Dr. Smith used to believe that benzene caused that translocation. The first time that we have heard that he had concluded differently now was when he appeared on the stand, which shows that predicting that what you are going to see is nothing more than hoping for something to happen in the future.

Thank you, your Honor.

THE COURT: All right. Thank you, all. I will take the matter under advisement.

MR. LEGHORN: Your Honor, we have worked out with the clerk and counsel that we're going to assemble a set of exhibits and get them to you next week.

THE COURT: Fine. Are you going to have the PowerPoint presentations on disk?

MR. LEGHORN: Yeah, we will have those. I have the copies --

MR. STEWART: If you want them on disk, that is how we'll provide them.

THE COURT: That will be convenient.

MR. STEWART: So what we have basically decided is our offices -- our offices will communicate with one another, come up with a plan, submit something that is court-personnel

friendly.

THE COURT: Good.

MR. STEWART: And thank you for your patience, your Honor.

MR. LEGHORN: Thank you, your Honor.

THE CLERK: All rise. Court is in recess.

(The proceedings adjourned at 2:55 p.m.)

C E R T I F I C A T E

I, Marcia G. Patrisso, RMR, CRR, Official Reporter of the United States District Court, do hereby certify that the foregoing transcript constitutes, to the best of my skill and ability, a true and accurate transcription of my stenotype notes taken in the matter of Civil Action No. 07-11944-GAO, Brian K. Milward, et al, v. Acuity Specialty Products Group, Inc., et al.

/s/ Marcia G. Patrisso
MARCIA G. PATRISSO, RMR, CRR
Official Court Reporter