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 3

John J. Moakley United States Courthouse
Courtroom No. 9
One Courthouse Way
Boston, Massachusetts 02210
Thursday, April 23, 2009
9 a.m.

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By Mr. Stewart		32		
JOHN M. BENNETT				
By Mr. Weathers	84		136	
By Mr. Stewart		114		137

P R O C E E D I N G S

THE CLERK: All rise.

Continuation of the Milward Daubert hearing.

Please be seated.

MR. LEGHORN: Good morning, your Honor.

THE COURT: Good morning.

MR. LEGHORN: If I may ask Dr. Garabrant to resume the stand?

THE COURT: Please.

DAVID HAY GARABRANT, resumed

MR. LEGHORN: Your Honor, I think I'm on the same input. I don't know if you're getting it or not.

THE COURT: I have it. Do you want everyone to have it?

MR. LEGHORN: Yes, your Honor. Please.

CONTINUED DIRECT EXAMINATION

BY MR. LEGHORN:

Q. Good morning, Dr. Garabrant.

A. Good morning.

Q. We ended up yesterday after the break in the court talking about the Golomb study. Other studies that Dr. Smith mentioned were studies done by Mele, M-E-L-E. Did you look at the Mele studies?

A. Yes.

Q. And what were your observations about the Mele studies

from looking at them?
A. I think I prepared a slide on that. Okay.
Q. Who is Mele, by the way?
A. Well, Mele is part of a group of investigators in Italy. The -- I believe he's with the Italian Leukemia Study Group, and they've published a number of papers, epidemiology studies, looking at leukemia.
Q. And did you look at those studies?
A. I did.
Q. And your observations about those studies, Doctor?
A. Well, the first point that's worth putting -- making is that one of the Mele publications, this one published in the American Journal of Epidemiology in 1994, provides some of the history of benzene use in Italy. And I've just taken a clip from that. It basically says in Italy the use of glues with a benzene content greater than 2 percent was prohibited by law in 1963. And then he goes on to say, "In our study, only two cases out of every 14 leukemia or RAEB cases who worked as a shoemaker began such work after 1963. Thus, significant exposure to benzene may have occurred, for most cases, before 1963, providing further evidence of a role for exposure to organic solvents."
Okay. So that's important history when we come to the study at issue.
Q. Was this a study that Dr. Smith referenced?

A. Well, he didn't reference this article; he referenced the next article by Mele.

Okay. So this is the one that Dr. Smith referenced. And this was published in 1995, but it's the same group of investigators. And what this article showed was that among APL cases, the center column, 5.7 percent of them were shoemakers compared to controls, the left-hand column, in which 1.5 percent were shoemakers. And then Mele calculates an odds ratio of 6.3, which is statistically significant.

Now, I have two points to make regarding that: This is actually a very small number of observations. Of the 36 APL cases, 5.7 percent represents two cases. So the observation's based on two cases. And it's important, if you go back and look at both of the Mele papers, to recognize that the cases were identified in 1987 to 1990. That actually matters, okay?

And then if you would click.

Okay. So if we recall from the other paper that benzene in glues was restricted in 1963. What's really going on in this paper is that substantial exposure was limited to a period at least 24 years prior to diagnosis, all right? Because the cases were diagnosed in '87 to '90, benzene use was restricted in glues in the shoemaking industry 24 years before that. And so this is inconsistent with a topoisomerase-induced mechanism, which Dr. Eastmond's paper says would act within two to 15 years of exposure.

Q. Doctor, a paper that -- do you have any other observations on the paper by Mele?
A. No.
Q. Doctor, one of the other papers that Dr. Smith talked about was the paper by -- Lois Travis published, that she published concerning the study of the Chinese workers; is that correct?
A. Yes.
Q. Did you have an opportunity to review that?
A. I did.
Q. Do you have any observations about that paper and Dr. Smith's analysis?
A. Yes, I do.
Q. And what are they?
A. If you could go to the next slide.

The Travis paper reported four cases of ANLL M3, as Dr. Smith's slide here points out, and they are -- if you look at the far right -- far left-hand column -- they are patients Number 5, 6, 7 and 8, okay? So in that paper they're recorded as M3, or APL. If you would click.

Okay. I went through the tables and the text in the Travis study to try to figure out how they made these diagnoses of M3. And what you see here is this little table I've prepared that summarizes the data from the Travis paper. Look at -- for Cases 5, 6, 7 and 8, looking at the peripheral blood

smear, the percent blasts, the peripheral blood smear morphology, the bone marrow percent blasts, the comments regarding what the bone marrow looked like, the cytogenics, immunophenotype, and the white blood cell count in the peripheral blood.

And when you -- it's a little hard to get all of this out of the tables, but when you put it together what you realize is that for Case 5 they didn't have any bone marrow examination; it appears that the diagnosis was based entirely on the peripheral blood smear morphology, which showed hypogranular promyelocytes. So it's my impression that that's not adequate to establish a diagnosis of APL. So that one, I think, is in serious question, and there's little reason to think that that's an APL.

Cases 6, 7 and 8 they did have bone marrow, and it's my understanding that the bone marrow was consistent with APL, but they did not have cytogenics or immunophenotyping on any of the these cases. And so this is not -- to the extent I'm aware, this is not adequate to really establish that these are APL cases, although Cases 6, 7 and 8, that's a reason -- I believe that's a reasonable decision, but that's certainly not a rigorous way of determining the diagnosis.

So --

Q. Okay.

A. -- one of these cases is unlikely to be an APL and the

other possibly or probably are.
Q. Doctor, in your answer you mentioned "phenotyping." What does phenotyping -- what information does that give you?
A. Well, immunophenotyping tells you about cell surface markers that helps you to identify the cell types.
Q. And what typing gives you the genetic karyotype?
A. Well, for APL, the -- a very high proportion of the cases have the translocation on Chromosomes 15 and 17 -- the t(15;17).
Q. Is that the cytogenetic testing that would give you that information?
A. Yes.
Q. Did you have any further observations with regard to the Travis paper and Dr. Smith's analysis?
A. Yes.
If you would go to the next slide.
Okay. So now the question is Dr. Smith's handling of the data in the Travis paper. Recall in the Golomb study Dr. Smith excluded one of the APL cases because the karyotype was normal. Remember, one of them didn't have the t(15;17), didn't have any abnormalities to 17. Dr. Smith excluded that case. Now in the Travis study he includes all four of these APL cases, and none of them had any karyotype done. In addition, as we're going to see on the next few slides, he actually creates five more APL cases that were not known to exist; they were not reported in

that study. And, of course, since they weren't in the study and didn't exist, as far as we know, they didn't have any karyotype, and they certainly didn't have t(15;17).

So my point is that Dr. Smith's arbitrary creating the data and choosing data, excluding a case in Golomb but now including cases that don't fit the rule he used in Golomb, is not a reliable scientific method and it is not a generally accepted methodology in the scientific community, neither in medicine or in epidemiology; he is simply creating data that fits his beliefs.

Q. Did you go through -- you mentioned that he created five cases. What did you mean by that?

A. I'm going to show you. I want to walk you through his calculations.

Okay. Here's his presentation of his calculations. This is from his slide. And, you know, instead of making what are relatively standard calculations of rate ratios, he does some fairly unorthodox things that are based on assumptions that I think are not reliable.

Okay. So these bulleted points, I'm going to walk through and show what these actually represent. If you would go to the next slide, please.

Okay. So the first thing is to abstract the data from Travis's text in Tables 1 and 2. If you read Travis carefully, what you see is in Table 1 there were a total of 82 cases of

lymphohemapoietic malignancies among which there were 32 cases of acute leukemia. Travis and her colleagues reviewed the pathology reports and medical records for 51 of the 82 total cases and 17 of the 32 acute leukemias.

Now, so they reviewed the diagnostic material from China, all right? In addition to that, they reviewed the histopathologic materials; in other words, they had the bone marrow biopsies, they had the pathologic materials. They reviewed those for 31 of the 82 cases including 14 of the 32 acute leukemias.

Now, there's a missing case of acute leukemia which can't reconcile with the Travis paper. You see the total of 32 in that first row. Seventeen of them they reviewed the pathology reports and medical records; 14 of them actually had the bone marrow -- the biopsy materials. There's one case unaccounted for.

Okay. If you look at the non-exposed workers -- I should have said we were talking about the benzene-exposed workers on the left.

If you look now at the right side of the paper with the non-exposed workers, there were a total of 13 total cases of lymphohematopoietic malignancies, six of which were acute leukemias. They reviewed histopathologic materials for three, and they saw one M2.

Okay. Now, if you would go to the next slide.

Q. Doctor, I've got a question here. On the benzene-exposed workers, under the 14 of the acute leukemias where Dr. Travis and her colleagues reviewed the pathology materials, you have another series of numbers: a nine, a four, a four and a one. Tell us what those represent.

A. Okay. Those 14 acute leukemias were broken down into the following subcategories: Nine of them were ANLLs, acute nonlymphocytic leukemia; five were acute leukemia not otherwise specified, AL NOS. Within the nine ANLLs, Travis and her colleagues felt that four of them were M2s, four of them were M3s, and one of them was an M4.

Okay. Now if you'd go to the next slide.

Okay. So here's what Dr. Smith does with that. He assumes that the proportion of all acute leukemias that were M3 can be obtained from the cases that had histopathological materials. So in other words, he says let's look at the 14 acute leukemias that had histopathology that Travis and colleagues could look at. There were four M3s. So four out of the 14 is 28.6 percent.

Okay. Now, I take issue with that assumption. And what he's going to do is he's going to apply that back to the 32, okay? What we have here is 32 acute leukemias. 14 had bone marrow biopsies; the others did not. People get bone marrow biopsies for non-random reasons, such as having access to medical care or better medical care, having an unclear

diagnosis that needs further evaluation. So it's not a reasonable assumption to think that the people who don't have bone marrow biopsies would have the same distribution of diagnoses as those who do. Furthermore, the diagnoses that were made by the treating physicians based on the pathology and medical records and whatever else they did to make the diagnoses and the review of those diagnoses by Travis I think would take precedence over Dr. Smith's assumption that he can now infer what the diagnoses were. The treating physicians did not reach -- or, say, there's no record that they reached any other diagnoses.

So if you would go to the next slide.

So what he does is he takes the 28.6 percent. He multiplies it times the 32 acute leukemias and says there must have been a total of 9.2 M3s in the total cohort of benzene-exposed workers. So in essence, where there were only four M3s diagnosed, he's creating 5.2 additional M3s that were not diagnosed and which Dr. Travis and Dr. Lee, who is a hematopathologist at the Mayo Clinic, did not feel -- or I should say made no decision existed [sic].

Okay. So if you would go to the next slide.

All right. Now he does the same calculation for the non-exposed workers. He says the proportion of acute leukemias that are M3 must be 28.6 percent. I'll multiply that times the six acute leukemias. That means there must have been 1.7 M3s

in the non-exposed workers. And again, I take issue with that assumption. I don't think that has any basis.

Q. Doctor, did Dr. Travis and her colleagues make an observation about the occurrence of M3 in both the exposed and the unexposed population?

A. Well, she doesn't comment on the unexposed, but, yes, she does comment on the four cases of M3 among the benzene-exposed workers.

Q. And what was that comment, do you recall?

A. I would have to go back and pull the paper to see it. I don't recall.

Q. Well, Doctor, do you recall whether she says that the incidence of M3 in the exposed population was similar to the de novo rate in the Chinese population?

A. Yeah. Thank you for refreshing my memory. She says on page 99, "Although AML-M3 occurred in at least four patients in this series, its general representation among the subtypes of ANLL was similar to its distribution in de novo ANLL in China," and she references reference 27. And if you go to her bibliography, 27 is a paper by Yang and Zhang in 1991 called "Incident Survey of Leukemia in China." Okay. And we'll come to that paper.

So she says, you know, the proportion of M3s among ANLLs in our study was similar to what was seen in China in the Yang paper. Okay.

Q. Did you do any further analysis of Dr. Smith's?
A. Yes. If you would go to the next slide.
Okay. Then Dr. Smith does the following calculation: He says, okay. Among the benzene exposed, there were 9.2 M3s out of a total of 74,828 people. And so let's divide that by the 1.7 M3s among 35,805 people. And that division yields a ratio of 2.59. So that's Dr. Smith's calculation. And he calls that an odds ratio, which it is not.
Q. And why is it not?
A. Well, it has nothing to do with odds. It's proportions; it's a different type of calculation.
Q. What's wrong with that?
A. Okay. So the entire calculation is based on the premise that Dr. Smith can diagnosis APL by imagining that it must have been present among people who were diagnosed and treated by physicians who did not reach this diagnosis and among people who, after careful review of medical records and pathology reports, were not diagnosed with APL by Dr. Travis and her colleagues at the NCI. Travis and her colleagues were responsible for the diagnostic validity in this major epidemiological study. Dr. Smith's creation of these cases is pure speculation; it has no basis in the paper.
Q. And does his approach that he's taken here -- is it consistent with methods and techniques used in the field of epidemiology?

A. No. I have not seen this done.

Now, there's an alternative that could have been done that I think is consistent with epidemiologic methods in common use, and that would have been to calculate the number of APL cases that would have been expected in the Travis cohort of benzene workers using the background rates of APL in the general Chinese population, and then it would have been reasonable to compare the observed and expected numbers. And this sort of calculation is routinely done in epidemiology to come up with either standardized incidence ratios or standardized mortality ratios.

So the idea is essentially you're saying, well, look, if the benzene cohort had the rates that are seen in the non-exposed population, how many cases would they have gotten? And then you say, okay. Here's how many we saw, compare it to how many we expected to see -- or how many we observed versus how many we expected to see -- and that's essentially a rate ratio. That's routine. And that's essentially what I showed when I taught the epidemiology methods yesterday.

Q. Doctor, you mentioned a study by Yang. And I'm going to --

MR. LEGHORN: Your Honor, this has been tendered to the Court as an exhibit to the brief. I don't know whether you would prefer that we mark it separately here, but I don't know if you have it.

THE COURT: If it's already in the record, it's not necessary.

MR. LEGHORN: Would you like a copy to follow along?

THE COURT: I could use it.

BY MR. LEGHORN:

Q. And, Doctor, you mentioned that you found -- or there was a source of the incidence rates in the general Chinese population; is that correct?

A. Yes.

Q. And you mentioned a particular paper, correct?

A. Yes.

Q. And what did you find in that paper?

A. Okay. Well, this is the Yang paper that Travis referenced as her Reference 27. And if you go to -- and it's an "Incidence Survey of Leukemia in China" published in 1991. If you go to Table 4 you will see that for M3, which is the fourth row in the table, the incidence rate is .35 per 10 to the 5th. So it's .35 times 10 to the -5, or 3.5 times 10 to the -6, which is 3.5 per million people per year. Okay. And that's in the range that Dr. Smith talked about of three to eight cases per million people per year. So this is an estimate of the rate in China. It's, to my knowledge, the only estimate available.

In addition to providing that rate, Yang also reports the percent of ANLL that is M3. And that's 18.7 percent. Now, we

saw in Dr. Smith's calculations that he assumed it was 28.6 percent, and I think that that's simply wrong.

Q. Now, Doctor, when Dr. Smith was on the stand, he was critical of using information drawn from the general population because it didn't account for the healthy-worker effect. Does Yang report on the population from which he gathered -- or that they gathered the data?

A. Yes. I didn't make a slide of this, but in Table 1 of the Yang paper, Yang lists the different populations that were surveyed in order to come up with this estimate of the incidence of the various types of ANLL. And there were 46 different areas in China where they do the survey. They calculate total person years of 60,557,127. So this is a lot of data.

And if you look down, what these -- at the list of what these populations are, about -- I don't know -- somewhere between -- I'd say roughly a third are working populations. So they come from the Daqing Oil Field, the Baoutou Steel Company, Yanji Forestry Farm, and so on. So some of these are general populations; some of these are working populations. So I think that's a reasonable way to collect the data.

Q. Doctor, can you explain how the healthy-worker effect may influence the results of epidemiological studies?

A. Yeah. Okay. The healthy-worker effect is a term that is used to describe the fairly common observation that working

populations have lower mortality than the general population, at least in the United States and Western Europe. And there's been a fair amount of investigation and thought about why working populations are healthier than the general population. And it varies from population to -- working population to working population. It's largely due to the selection of healthy workers at the time of hire.

So in the United States and Western Europe, it was a general practice to hire healthy people and to not hire people who had preexisting diseases, people with low-back problems, people with orthopedic problems, people with heart disease. You know, that was common, okay? Now, that's actually gone away, in part, because of the Americans with Disabilities Act. You can't do that anymore in the United States. But it was done, all right?

The real question is, does the healthy -- you know, if we're going to talk about leukemia, and particularly M3, can you select people at the time of hire with any idea who's going to not get APL or acute leukemia? And the answer is: You can't. You can't select people at the time of hire because we don't know what -- we don't know who's at increased risk for leukemia.

So the idea there ought to be some adjustment for the healthy-worker effect for leukemia really has no basis. If you were talking about a study of orthopedic problems, then I would

say, yeah, you really would have to pay attention to the healthy-worker effect; if you were talking about a study of cardiovascular disease, where you can select people who are at lower risk of cardiovascular disease -- and essentially you would be selecting against smokers and people with high blood pressure and people with uncontrolled diabetes and people with hypercholesterolemia -- yes, you can select against people who had increased risk of future cardiovascular disease. But you can't do it for leukemia. So I don't think there is any healthy-worker effect for this diagnosis.

Q. Doctor, using the Yang data from this article, did you do any calculations?

A. I did. Okay. So I calculated the expected number of APL cases, or actually, I should say the number of APL cases you would expect to occur in the benzene cohort if they had the background rates seen in the general population of China from the Yang paper. So what you do is you take the number of person years in the -- actually, I made another typo -- I apologize -- the number of person years in the benzene cohort, and that's reported as 782,368, and that's in another one of the papers by Travis and her colleagues; you take the incidence rate in the -- from the Yang paper, which is 3.5 times 10 to the -6; and then you multiply those two numbers together to get the expected number of APL cases in the benzene cohort. And you would expect about 2.74 if they had the same rates as the

general population.

Then I calculated rate ratios. And I did it two ways. I said, first off, let's assume that all four of the APLs that Travis diagnosed were APLs. So we observed four, we expected to see 2.74 based on the background rates, the ratio of 4 over 2.74 is 1.46. I calculated a p-value for that, it's .29, and I calculated the 95 percent confidence interval, which is .4 to 3.74. So there is a -- let's say a moderate association that is not statistically significant and the confidence interval includes one. So, okay, there's a small association.

I did the calculations again based on three observed cases; in other words, eliminating one of them that I think is unlikely to have been an APL. This time you get a rate ratio of 1.09, so it's almost 1, p-value of .52, and the confidence interval goes from .23 to 3.20.

If you would click again.

Okay. So these results indicate there is no significant association between benzene exposure and APL in the Travis paper. And it doesn't matter which calculation you use, whether you use the four or the three observed, you still come out with a result that is nowhere close to statistical significance.

Q. Doctor, did you do a calculation taking into account or making some attribution for a healthy-worker effect?

A. Yes, I did. I said, okay, if there were a healthy-worker

effect -- and here you have to have some background knowledge of the magnitude of the healthy-worker effect. In the U.S. and in Europe we commonly see healthy-worker effect that range from none to about a 30 percent reduction in mortality, okay? So working populations may have only 70 percent of the mortality of the general population -- in some settings.

So I said, okay. Let's adjust for that. Let's bump up the observed by 25 to 33 percent -- so add one case to the four, that would be a 25 percent adjustment for the healthy-worker effect, or add one case to the three, that would be a 33 percent adjustment. I did that -- it increased the rate ratios in both of those calculations; the p-value was still nowhere close to significant.

So even if you make an adjustment for the healthy-worker effect, which I don't think is appropriate to do, you do not have a statistically significant association in this data set.

Q. Did you do any further calculations with regard to any of Dr. Smith's calculations?

A. No, I think that was everything.

Q. And, Doctor, at this point can you summarize your observations with regard to Dr. Smith's methodology and their consistency with epidemiological methods?

A. Yeah. It's my view that Dr. Smith's methods for choosing data and excluding data is arbitrary and unreliable. His methods for analyzing data are arbitrary, they're not reliable,

and they're not accepted in the scientific community. These are not the sorts of calculations we see.

Number 2, none of the authors of the studies he cites -- Rinsky, Glass, Travis, Golomb -- made any of the calculations Dr. Smith made, nor is there any information in those papers that supports any of Dr. Smith's methods for choosing the data as he did or for analyzing the data as he did.

Number 3, Dr. Smith made a number of errors and misrepresentations. Number 4, the reliability of the methods he uses is not known and to my knowledge has never been tested. Number 5, much of the evidence he relies upon has nothing to do with benzene and APL; it either addresses other diseases or it addresses other exposures. So it is not relevant to the issue of whether benzene causes APL.

Number 6, Dr. Smith has failed to show any reliable evidence that benzene is associated with APL. And Number 7, Dr. Smith ignores the evidence that shows no association between benzene and APL. He simply doesn't look at it.

Q. Now, Dr. Garabrant, in your work, you've become familiar with the Hill criteria?

A. Yes.

Q. And in your work, have you been involved in studies exploring the issues of cause and effect of exposure to an agent and the potential development of a medical condition?

A. Well, much of the work I've done over my career has been

focused on that issue.
Q. And did you, looking at what Dr. Smith did, consider that in connection with the Hill criteria?
A. I did.
Q. And using the Hill criteria, do you have an opinion as to whether there is adequate evidence to determine whether benzene is capable of causing APL?
A. I do.
Q. And what is that?
A. Okay. If you'd go to the next slide. Well, actually, we'd have to go to the next one.

I wanted to point out -- I think I already covered this earlier -- the claim was made that John Snow didn't need statistics to take the handle off the Broad Street pump. And this is right out of Hill's paper. John Snow, in fact, did use statistics to calculate the death rates, which we would call mortality rates, in different regions of London. And he figured out which regions were supplied by which water supply. And it was quite clear -- and this was using statistics as they were available in 1855. It was quite clear that the death rate in some areas of London, which were supplied by water from the Thames downstream of the city, was dramatically higher than the regions of London that were supplied with water from the Thames from upstream of London.

So he did use statistics. They were rudimentary compared

to what we do today, but he did.

Okay. Next slide.

Q. Doctor, looking at a 14-times increase given what Dr. Snow observed, would it be fair to come to a cause-and-effect relationship with regard to the wells without doing the techniques that we do today?

A. Well, I think you've asked two questions, and you've got to separate them out. It would certainly be fair to come to a conclusion that there was a very strong association between the source of the water supply and the risk of death from cholera. That is quite clear. And you don't really need a p-value; it's obvious.

Okay. As to whether you would make a causal determination, I think you would want to step through the considerations that Hill puts forth. Okay. So it's more than simply saying, "Gee, I've got numbers." You have to think about what the numbers mean.

Q. Now, going through the Hill considerations with regard to Dr. Smith's observations, what did you conclude?

A. All right. So these are Hill's considerations. The first is "Strength of Association." You have to have an association. And Hill says stronger associations are less likely to be due to subject errors like bias and confounding. So the question is how large is the association between benzene exposure and APL --

If you would click.

-- and the answer is none. We don't have an association, period. Okay.

Hill next says, well, has this association been observed consistently by different persons; in other words, different investigators in different places in different circumstances, different times? And the answer is no, we don't have any consistent association.

Third, he asks, is the association limited to specific workers and to particular sites and types of diseases? And the answer is no, we don't have an association.

Number 4, temporal relationship: Which is the cart and which is the horse? Well, hold on. You've gone ahead of me there.

The answer is, yeah, we have temporality in all of these studies; we know whether the benzene preceded the diagnoses. Okay. So we have temporality.

Okay. Five: Biological gradient, which we call "dose response." No, there is no dose response. There is no study that shows the risk of APL increases with increasing benzene exposure. None.

Okay. Number 6: Plausibility. Okay. Now, Hill's cautious about plausibility. He says, "Is the causation we suspect biologically plausible? This is a feature we cannot demand. What is biologically plausible depends on the

biological knowledge of the day." All right. I think this is questionable.

So if you would click on that.

Q. Doctor, Dr. Hill also, with plausibility, says you shouldn't reject an association even if you can't understand what's bringing it about.

A. Absolutely. So if you see a strong association -- if you see dose response and you can't explain it based on your biological understanding of the disease -- you should not reject it, okay? But he doesn't say that you should continue to consider that an association is plausible when you can't find an association, okay? And I think this is -- plausibility is not satisfied. You know, what we heard about yesterday from Dr. Cranor is the way the NTP and IARC assess data. And they rely heavily on human epidemiology studies but they're also willing to consider mechanistic evidence; they're willing to consider animal evidence.

So if I were to look at plausibility here for benzene and APL, I would consider the following: First off, we don't have epidemiologic evidence that supports it; in fact, we have epidemiologic evidence that says there's no association. Secondly, we do not have any evidence that benzene causes translocations of Chromosomes 15 and 17, which is essential. Don't have it.

Thirdly, I'm not aware of any animal model that

demonstrates benzene causes APL. And, fourth, I'm not aware of any mechanistic evidence in any cell culture, in any animal, in any setting that gives us a mechanism by which benzene can lead to APL. We don't have the steps.

So I would say, you know, thinking in the way Dr. Cranor did yesterday, well, could we rely on other forms of evidence? The answer is we don't have any other forms of evidence, and the epidemiology says there's no association. So I think it's implausible.

Q. Coherence?

A. Coherence. All right, Hill says, "The cause and effect interpretation of our data should not conflict with generally known facts of the natural history and biology of the disease." And my answer is that there's no conflict here; there's no evidence that benzene causes APL.

Okay. "Experiment: Do we have experimental evidence that preventative action does, in fact, prevent the disease?" No, we don't. And then "Would it be fair to judge by analogy?" I don't think so.

Okay. So I don't think that this set of information satisfies Hill's criteria in any way with the exception of we know in these various studies that benzene preceded the various diagnoses of lymphohematopoietic leukemia.

Q. Or at least the way Dr. Smith interpreted the study. He didn't know whether it was actual benzene exposure.

A. Well, in the studies that look at benzene, we do -- and remember, we have Yang; we have Rinsky -- I mean, the two studies that really are pure benzene-exposed, they don't support it; they don't show it.

Q. And, Doctor, finally, Dr. Smith mentioned a study by a Joli Weiss concerning acetaminophen use and risk of adult leukemia; is that correct?

A. Yes.

Q. Did you have an opportunity to review that?

A. I did.

Q. And do you have any observations on that?

A. This study was reported in Leukemia Research in 2006. It came from Roswell Park Cancer Institute in Buffalo, which is a very fine institution. And what it says is that at Roswell Park they ask every patient to fill out a 16-page questionnaire regarding a long list of things. And they've analyzed that. And what they found was that there was a positive association between ever having used acetaminophen, so Tylenol and other drugs like that -- or I should say "and other products like that" -- the odds ratio was 1.53. The confidence interval went from 1.03 to 2.26. And they found a weak inverse association with aspirin use, which I think was not statistically significant.

Okay. When they looked further at the acetaminophen data, they did not find any evidence of increasing risk with the

frequency of acetaminophen use with the degradation of acetaminophen use or with the cumulative acetaminophen use. So what we have is an association. We don't have dose response; we don't have a body of results that presents a consistent picture.

I would say this is a suggestion. It's -- if we went back to the scientific method, I would say this is a basis for a new hypothesis that needs to be tested. And I think the author's basically said that in their discussion. "Gee, this is brand-new. It certainly needs to be confirmed by other studies." It's an awfully important issue. If we think that acetaminophen causes adult acute leukemia, that's a big issue.

And so I would say this is a hypothesis that really deserves a rigorous evaluation and further testing before we should make any further conclusions about it.

Q. And did they conclude there's a cause-and-effect relationship between acetaminophen and leukemia?

A. No, I think they're appropriately cautious and do not make that conclusion.

Q. Thank you, Doctor.

MR. LEGHORN: No further questions, your Honor.

THE COURT: All right.

Mr. Stewart, are you going to be using any of the equipment?

MR. STEWART: I will. I will be using the Elmo.

THE COURT: Okay.

CROSS-EXAMINATION

BY MR. STEWART:

Q. Good morning, Dr. Garabrant.

A. Good morning.

Q. I'm not going to attempt to cover everything you covered or we'll never finish this week, and I want to finish this week, so I'm going to try to focus on some of the things that you covered. But first, before I do that, I would like to spend some time with a document that you ended up producing about the testimony that you've given over the last five years, all right? And what I would like to do is I would point out -- and this makes sense because you filled this out November 19, 2008 -- that this chart stops November 18, 2008. So it was very, very current up to that time period. Thank you for doing that. I want to go through this list in a summary fashion and then try and have you update it so we have a better understanding of how often you do this, all right?

So with respect to this list, I counted some 62 times from November 2004 to November 18, 2008, where you gave deposition testimony or trial testimony in some form or fashion in a legal context, fair?

A. Yes.

Q. Okay. Now, what is your current occupation?

A. I am emeritus professor of Occupational Medicine and

Epidemiology at the University of Michigan.
Q. Okay. And does that mean you're still on the payroll?
A. Yes.
Q. Okay. What are your duties in connection with that?
A. I have an active research agenda. We're running one very large study, and I have three other studies we're still writing papers and analyzing data and reporting at.
Q. Okay. Now, in the year 2008, how much money did you make doing this kind of work, being an expert in litigation?
A. I don't know exactly. I would estimate it was probably in the range of 400-, maybe $450,000.
Q. And of that $450,000 that you made in 2008, how much of that as a percentage came from giving testimony or doing work on behalf of companies in a toxic tort context?
A. I'm not sure I could break it out in a toxic tort context. It -- I believe it was all defense work.
Q. Okay. So in 2008 450-some thousand dollars for this type of work. How about in 2007? How much money did you make in 2007 doing this kind of work for companies in the defendant role?
A. Again, I don't know exactly. I believe it was less in 2007. I would estimate 300- to $400,000.
Q. Okay. So now let's talk about --
MR. STEWART: Your Honor, would you mind if I go to the chart, please? Thank you.

BY MR. STEWART:
Q. So in 2008 we were at $450,000. I believe in 2007 you gave us a range -- and I don't want to get it wrong. What was the range you gave us?
A. I think I said 300- or $400,000.
Q. And in 2006 what would be your estimate of the amount of money that you made doing this kind of work on behalf of defendant companies?
A. I don't know. I believe it would have been less. I would have to guess at this point. I don't actually know.
Q. I don't want you to wildly guess, but if you could give us a reasonable estimate, that would be --
A. It was probably in the range of $300,000.
Q. Okay. And then in 2005 -- and we'll stop there for the sake of time -- give us a reasonable estimate of the amount of money that you made doing this kind of work for defendant companies.
A. To be honest, I don't know. I mean, it was appreciable. I don't know whether it was 200- or 300- or 350-. I just don't recall.
Q. Okay. So --
A. I don't know.
Q. -- let's do this: Conservatively $200,000?
A. Yeah, that would -- it was above that.
Q. Okay. More than $200,000.

So over the past four years it's safe to say that you have made more than $1.2 million doing this kind of work; fair?
A. Yes.
Q. And it could even be more than $1.6 million doing this kind of work for companies, correct?
A. I don't know. I mean, those numbers don't total to that. I'm not sure.
Q. $1.3 million?
A. Yes.
Q. All right. Now, in connection with these sums, is it fair to say that over the last -- from 2005 to 2008 that this is the manner in which you make most of your money?
A. It's varied. In some years, yes; in some years, no.
Q. In 2008 was it the manner in which you made most of your money?
A. Yes.
Q. How about 2007? Was this the manner in which you made most of your money?
A. No.
Q. Okay. How about 2006?
A. I'm not sure. To be honest, I don't know.
Q. Okay. Now, I told you that I realize this was as up-to-date as you could possibly be, and to be fair there was one thing that wasn't on here which was a trial you and I were involved in in California, true? Turner versus Chevron?

A. Yes.
Q. But to be fair, Turner versus Chevron -- your deposition is on this list -- it looks like you just inadvertently left off the trial portion of that. No big deal. I want to ask this question, though: If we were to update this list from November 18, 2008, to the present -- we have 62 things up to November 2008 -- how many more items would go on this list from November 18, 2008, to when you came into this courtroom and began testifying yesterday?
A. I would estimate -- so that was a five-month period, a little less than half a year -- if you took 2008, and took about half of the number for 2008, that would be a reasonable estimate for 2009.
Q. Does that mean that you're doing more of this on a monthly basis in 2009 than you were doing in 2008?
A. No, I think about the same. You use about the same rate.
Q. Okay. So in connection with the year 2009, if we put 2009 on the board as well, how much money have you made or billed in 2009 in relation to doing this kind of work for defendant companies?
A. I would estimate somewhere between 150- and $200,000.
Q. Now, it's true that you haven't published any studies of benzene-exposed workers and leukemia risks, true?
A. I'd have to look at my CV. I think my colleagues and I, when I was at the University of Southern California, did a

number of studies where the answer would be yes. We did a study of workers who had a high exposure to electromagnetic fields in -- which we assessed their benzene exposures and we reported out their leukemia risks. The goal of that study, however, was to look at leukemia in relation to electromagnetic fields, but benzene was a potential confounder.

We also published a study of childhood leukemia in which we looked at parents' occupations and parental occupational exposure to solvents including benzene. And I've done other studies that are not yet published that have also looked at that issue.

Q. When you say "not yet published," they're in the queue to be published or they just weren't published?

A. In the queue. I haven't gotten around to writing the manuscripts yet.

Q. Okay. So in connection with these at issue, have you published any article, textbook, chapter, any publication in which you've expressly discussed the issue of whether benzene exposure is capable of causing some subtypes of AML but not others?

A. No.

Q. Now, I want to turn to something that you said yesterday. I want to get to the heart of some of the things that you have testified about. And the first thing that I want to do in that category is I want to talk about your discussion of Rinsky and

what Rinsky said. So I'd like to do it this way. You were asked this question by Mr. Leghorn yesterday and, Dr. Garabrant, I am reading from the transcript which everybody's getting on a daily basis here. You were asked this question --

MR. STEWART: Your Honor, is that light enough here?

THE COURT: Yes.

MR. LEGHORN: Thank you.

BY MR. STEWART:

Q. You were asked this question: "And, Doctor, do you have an opinion whether Rinsky supports the conclusion or that Rinsky -- the Pliofilm cohort supports the data there" -- "supports the conclusion that benzene causes APL?" And you said, "Well, it does not. There is no case of APL in that cohort."

That was your testimony, correct?

A. Yes.

Q. And in addition, what you did was you had a slide that you showed -- and I've got a black-and-white of this slide. And you showed the slide and said in 1981, the Rinsky study, a single case of leukemia coded ICD 205 was acute myeloblastic leukemia, not APL. Then you brought out this slide and said in the 1994 updated data, two cases of leukemia were coded to 205.0; neither was diagnosed as APL. "Dr. Smith claims the AMLs could have been APL, but he doesn't know."

That's what you put, correct?

A. Yes.
Q. Now, in connection with the Rinsky case and in follow-up to the Paxton, here's my question: How did you know that the AMLs were not APLs?
A. I don't. The point is they were not written down as APLs; they were written down as acute myelocytic leukemia. It would be speculation to infer that they were something also.
Q. Well, it would be actually speculation to say that there is no case of APL in that cohort, wouldn't it?
A. There is no case of APL identified in that cohort.
Q. That doesn't mean there's not an APL in that cohort, does it?
A. The Paxton paper reports what the diagnostic information was. That's all there is to go on. So there could be an APL there, but there's no information that says there is an APL there.
Q. Well -- and this is because you'd have to write down on the death certificate what the subtype of AML was, correct?
A. In order for the Rinsky paper or the Paxton paper to know the diagnosis, it has to be written on the death certificate.
Q. So what I said was correct, right?
A. Yes.
Q. Uh-huh. And when we look at the Rinsky paper -- this is page 240 of the Rinsky paper -- it says -- Case 3 was in a 60-year-old male who died in 1958; the cause of death, recorded

on the death certificate, was acute myelocytic leukemia, correct?

A. Yes.

Q. Now, that's not a subtype, right?

A. Well, that could be all that the diagnosis provided. There are many patients where that's what the hemopathologist said it is. That's it.

Q. Just answer my question, sir. That is not subtyped, correct?

A. It does not give one of the FAB subtypes. And sometimes you can't reach a further diagnosis. So it is what it is.

Q. Well, so that part that you just put there with the comma, sometimes you can't reach that, you don't know if that was the case here or not, correct?

A. That's correct.

Q. So this is an example of something that could have been an APL, might not have been an APL; we just don't know, correct?

A. I certainly don't know. All you have is what's written on the death certificate.

Q. Right. So Rinsky doesn't know, true?

A. I assume Rinsky doesn't know.

Q. Dr. Paxton doesn't know?

A. All any of us have, to my knowledge, is what's on the death certificate.

Q. Yes.

A. That's it.
Q. So when you came yesterday and said that there were no APLs in that cohort, that was an overstatement of what the scientific evidence was showing, correct?
A. I think that was a fair statement.
Q. Well, it's only a fair statement if you can say that people looked for APLs and identified them when they found them in subtyping, correct?
A. Well, it would have been fair to have said there were no APLs recorded on the death certificates.
Q. Right. And then it would have been fair to say, "So we cannot say whether or not there were APLs," correct?
A. I cannot say whether there were or were not APLs. All I can say is that there were none recorded.
Q. Uh-huh. So I'm back to this slide. When you say Dr. Smith claims the AMLs could have been APL but he doesn't know, he was accurately describing the Rinsky article, wasn't he?
A. Well, I think that that's going a little beyond what Rinsky said. I mean, you know, you've got written records that come from death certificates. They say what they say. If you want to say, you know, "I really think that these were something else," I think that's going beyond what the death certificate says. That's it. So, I mean, I don't think Dr. Smith knows that they were APLs, nor do I. I don't know they weren't APLs. All I know is what was recorded and presented in

the Rinsky paper; that's it.
Q. Yes, I agree with you, Dr. Garabrant. But you're making the insinuation that Dr. Smith came and said that the Rinsky paper said there were APLs. Did you hear him say that?
A. I'm not sure -- I don't understand the question. I said the Rinsky papers said there were APLs?
Q. I'll rephrase it. This statement right here by Dr. Smith, you say Dr. Smith says he doesn't know whether there were APLs or not, correct?
A. Okay. We're going to parse the words. I think what I'm saying there is Dr. Smith claims the AMLs could have been APL. I am saying he doesn't know. I didn't mean to say that Dr. Smith said he didn't know; I'm saying that I don't think he knows. Maybe I should have written that a little differently.
Q. And were you trying to infer from this that he said he did know?
A. No. To the best of my understanding of what he said, he said they could have been APLs. And my comment is he doesn't know.
Q. Well, isn't it true that you agree they could have been APLs?
A. It's possible that the ones that were coded to ICD 205.0 using the ICD-9 could have been APL because APL is coded to 205.0 in the ICD-9. So it could have been.
Q. Well, there are some things that are coded to 204 that

could have been APLs, too, aren't there?
A. Which ICD is that?
Q. It's 204.
A. No. No. Which version of the ICD is that?
Q. This was 7.
A. Then you would have to go back to the ICD-7. I'm not sure I recall it from memory, but I think the coding changed. I think under ICD-7, a 204 was acute myelogenous leukemia. But we would have to pull up the ICD-7.
Q. Well, let's just look at what Rinsky actually says. What Rinsky says -- and let's go back to Case 3, since we were looking at that before -- Case 3 was in a 60-year-old male who died in 1958. The cause of death recorded on the death certificate as acute myelocytic leukemia was coded as ICDA 204, right?
A. That's what it says.
Q. Yes. And that could have been APL, true?
A. Conceivably it could have been.
Q. So when you said maybe the 205s, in fact, some of the 204s could have been APLs as well, right?
A. Okay. Could you go back to Paxton's table?
Q. I can.
A. Well, I mean, what you're talking about now is the reclassification of the ICD-7 to the ICD-9. They changed the codes. This is from memory; I don't memorize the ICD versions.

I think in the ICD-7 AML was coded to 204. I think in the ICD-9 it was coded to 205.

Now, the question is, when Travis presented those ICD results, did she update them all to 209 or did -- or to the ICD-9, or did she leave them with the original codes and indicate that these were the original codes from the ICD-7, the ICD-8, the ICD-9? I can't --

Q. So you don't know?

A. Well, not from memory, I don't know. Could you put the chart up?

Q. I can.

A. Okay. And what's her footnote say? Okay. So her Footnote A says, "International Classification of Disease Code currently on the 1987 update of the NIOSH tape." And if we look back -- if we look at the top half where we see some of the 204s are written as acute myelocytic leukemia/acute myelogenous leukemia, that would suggest to me those are the ICD-7 codes in which AMLs were coded to 204.

Q. Yes.

A. Okay.

Q. So what I said earlier about the 204s, things that were coded as 204 could also have been APLs, correct?

A. Well, they are what they were written as, and conceivably some of them may have been APLs.

Q. Well, let's look at how Rinsky recorded them so there's no

misunderstanding. Case No. -- we already talked about Case No. 3. Let's look at Case No. 4. It says Case 4 was in a 65-year-old man who died in 1960. The cause of death, recorded on the death certificate as, quote, "acute myelogenous leukemia," was coded as ICDA 204, correct?

A. That's correct.

Q. Case 4 is another example of someone in the Rinsky study who could have been an APL, correct?

A. Could have been.

Q. Let's look at Case No. 6. Case No. 6 was a 57-year-old man who died in 1961. The cause of death recorded on the death certificate as acute granulocytic leukemia was coded as ICDA 204. That is another example of someone who could have been an APL, correct?

A. You know, as far as I know, it could have been. I think before it is fair to do this, we should get the ICD-7 in front of us and see where APL is coded, okay? Because I don't know where APL's coded in the ICD-7.

Q. Well, now, wait a second, Doctor. In order to be fair, before you came and gave testimony to this Court it was only 205 that APL would have been in, shouldn't you have already done that?

A. My point was that in not one instance in the Rinsky paper, or the Paxton paper, was APL diagnosed. So it's not critically important to know which ICD code they're coded to. The point

is there is nothing recorded there as APL. If you're going to take me through now which codes in which ICD revisions would have been AML and could they have been APL, then I have to go back and look at the ICD-7 and say, well, where would APL have been coded? In other words, there's an inference here that the coding was right and that when you say 204.1, that that not only included acute myelogenous and acute myeloblastic and acute granulocytic, but that that code also included acute promyelocytic leukemia. And I'm saying my memory isn't that good. I don't know whether they would have all been coded 204.1 in the ICD-7.

Q. You just said that no one in the Rinsky-Paxton study was diagnosed with APL. That's what you just said, correct?

A. I said what I said. Nobody was recorded as having been diagnosed with APL.

Q. Okay. But that's different than being diagnosed with APL, isn't it? Because this is a study where you have -- the recordation is something is written on the death certificate. This is all we have: what's written on the death certificate and the ICD code, correct?

A. That's correct.

Q. Okay. And so if there's not an ICD code for APL in ICD Code No. 7, there's nowhere to put "APL," is there, in its own distinct category?

A. I'm not sure I understand. "In its own distinct

category." What do you mean?
Q. Well, isn't it true, Doctor, that it wasn't until the ICD-10 codes that APL was recognized with its own distinct ICD number?
A. It is correct that under the ICD-9 APL was coded to 205.0. It's also correct that the ICDO system, which was created by the World Health Organization and public in 1986 to allow more precise coding of cancers, had clearly identified a unique code for APL. So the ICDO, it was there. And I've been a cancer epidemiologist since the late '70s. The ICDO made it quite clear you could code APL as a distinct diagnostic category as early as 1976, and then for those who were doing this, well before that.
Q. Hmm. So you're saying that you believe there was an ICD code for APL that could have been used in the Rinsky study specifically. That's what you're saying?
A. I said ICDO.
Q. Uh-huh. ICDO is not ICDA, correct?
A. That is correct.
Q. Uh-huh.
A. The ICDO is a classification system for cancers put out by the World Health Organization in addition to the ICD system.
Q. Yes. But the ICDA is what is recorded in Rinsky, correct?
A. Well, what's recorded in Rinsky is the cause of death. That's what's important.

Q. No, Doctor, what's recorded in Rinsky is both the cause of death and a code, ICDA 204, right?
A. Correct.
Q. Okay. So when you said "ICDO codes," those aren't the codes that are being used in the Rinsky paper, are they?
A. That's correct. Your question was whether there was a unique code for acute promyelocytic leukemia prior to the ICD-10, and my answer was, yes, there was.
Q. But the codes that are being talked about in Rinsky and Paxton, these papers you've looked at, are not that code that you've just mentioned, are they?
A. No. They're the ICD-7 or ICD-8 or ICD-9.
Q. Yes. Thank you. So now going back to other cases, Case 10 was in a 38-year-old male who died in 1955. The cause of death recorded on the death certificate as acute myelocytic leukemia was coded as ICDA 204. That's another example of someone who could have been an APL, correct?
A. Could have been.
Q. And 12, Case 12, 48-year-old male died in 1954, diagnosis was acute myelocytic leukemia. That's another example, correct?
A. Could have been.
Q. Someone who could have been an APL?
A. Could have been.
Q. Okay. Now, I want to go to a different topic. And the

topic I want to go to now is the Travis paper. And the Travis paper -- what you said in the Travis paper was there were four APLs that were listed in the Travis paper. And I'm going to put that chart up. It's Table 4. You said it was 5, 6, 7 and 8, correct?

A. Yes.

Q. And let's just make sure we're clear here on the Travis paper. These folks -- and we're looking at, I think, 12 authors on the Travis paper, correct?

A. Yes.

Q. All right. And these 12 authors who are studying this group of people have reached the conclusion from the evidence that they are looking at, 12 people looking at this evidence, that they believe four of these people are best classified as APLs, correct?

A. That's correct.

Q. And you disagree with them, correct?

A. I think that Case 5 has very scant information upon which that diagnosis is based; that's all.

Q. I understood that. But there's 12 people who came together, looked at the evidence, wrote a paper, true?

A. Yes.

Q. And those 12 people had that paper peer-reviewed by other people, true?

A. As far as I know.

Q. Who looked at the same kind of information that you looked at, right?
A. Well, they had the manuscript; yes.
Q. Exactly. And those 12 people and their peer-reviewers -- and in those peer-reviewers there was an editor of that journal in addition to the peer-reviewers, true?
A. Yes.
Q. All right. And so with 12 authors, peer-reviewers and editors who came to the conclusion that this information was a fair and accurate representation of what they saw and what they found, you've basically come to say you disagree with it, correct?
A. I think, as you saw in my presentation, that I did my calculations assuming that there were four APLs, and I did them again assuming there were three, because I think the diagnosis of Case 5 is uncertain -- is based on uncertain data; nonetheless, I will defer to a qualified hematopathologist to make that decision.
Q. Well, Dr. Garabrant, so I'm clear, you are unwilling to defer to 12 experts who looked at all the data, collected it, analyzed it, presumably talked about it, came to conclusions about it, put it in front of peer-reviewers, put it in front of an editor, put it out there for the world to see -- you are unwilling to defer to them to say that their conclusion is a reasonable one, true?

A. No.
Q. That's not true?
A. As you saw in my presentation, I considered that they were right. I included all four cases. I also considered that one of them, based on reasonable grounds, might not be APL. I did it both ways. The point of my presentation was to show that you can get a significant association either way.
Q. But you do get an association, correct?
A. Uh-huh.
Q. And these Bradford Hill considerations that you were talking about, the Bradford Hill considerations don't talk about a significant association; they talk about the strength of an association, true?
A. No.
Q. That is not true?
A. That is not true.
Q. So let's look at what Bradford Hill says. It says, "Strength. First upon my list, I would put strength of association." That's what it says, right?
A. It's one of the things it says, yes.
Q. Yes. It doesn't say "significant"; it says "strength," right?
A. Well, it is talking about associations, and the strength of the association matters.
Q. I don't disagree with you. "Under this same heading of

'Strength of Association,' Hill said we must nevertheless look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed [sic] observation appears to be slight. There are many occasions in medicine when this is in truth so."

That's what Hill said, right?

A. Well, you're missing one of Hill's important points which is that you must assess the play of chance, okay? That's woven throughout the paper. He's talking about once you have done an appropriate assessment of the play of chance, then you look at strength of association and dose response and consistency, et cetera.

Q. Well, that's funny, Doctor, because he doesn't get to chance until later in the paper. He first talks about strength of association and then he talks about the -- this concept of don't be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. That's what he said, right?

A. Well, yes. And you certainly wouldn't accept a slight association that was entirely compatible with chance. If you read his article carefully, you'll see that quite clearly. You don't accept weak associations that are chance or are entirely compatible with chance. He has a whole section on tests of significance after he finishes the nine considerations.

Q. Yes, there are. I agree with you.

A. Right.
Q. It says, "Tests of significance. No formal tests of significance can answer those questions."
That's what he says, right?
A. Yeah. Then if you want to interpret that, you have to go back to what the questions are.
Q. Uh-huh. Well, he says here --
A. If you'd read the paragraph just above that.
Q. I'm happy to. Just above it? "Here then are nine different viewpoints, all of which we should study" -- "all of which we should study association before we cry causation. What I do not believe, and this has been suggested, is that we can usefully lay down some hard and fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis, and none can be required as a sine qua non. What they can do with greater or less strength is to help us to make up our minds on the fundamental question: Is there any other way of explaining the set of facts before us, is there any other answer equally or more likely than cause and effect," correct?
A. And then he talks about tests of significance, which means you have to evaluate chance as a possible explanation that is more likely than cause and effect.
Q. Well, actually, he says there's no formal test of chance.

That's what he says, right?
A. There's no formal test of significance that can answer those questions, but the point is you have to address it.
Q. But, Doctor, you have been using a formal test of chance the entire time you have been in this courtroom, haven't you?
A. Hum?
Q. You've been using a formal test of significance, and your formal test of significance is the 95th percent confidence interval or the P at .05. That's your formal test, correct?
A. No. No. I've been doing exactly what Hill says you must do, okay? "No formal tests of significance can answer those questions. Such tests can and should remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects." In other words, what he's saying is before you accept that there is a causal association, you've got to assess the role of chance, you have to -- and it will instruct you in the magnitude of the effect of chance.

Now, as to whether you choose a p-value of .05 or a p-value of .04 or a p-value of .01 as your nominal threshold for statistical significance I think is arguable. By convention we use .05. My calculations show repeatedly that you're nowhere close to .05; you've got p-values of .2 and .3 and .5, okay? These results are entirely compatible with chance findings; they are not indicative of cause and effect.

This is chance stuff. That's what Hill says you need to do.
Q. Okay. So you didn't share with the Court all the calculations you did on the Travis study, did you?
A. Well, I spent quite a bit of time trying to figure out what Dr. Smith was doing, and I tried to make calculations trying to follow his reasoning in addition to the ones I presented. I'm not sure what you're referring to.
Q. I'm referring to this slide right here. That starts, "It is possible to make other more plausible assumptions about the cases of APL in the Travis cohort. These would yield different estimates of the association between benzene and APL."
This is your slide, right?
A. Yes.
Q. Didn't show this one to the Court, correct?
A. I did not.
Q. Uh-huh. And in this slide what you did is you made an assumption that 18.7 percent of the AMLs in the Travis study were APLs, right?
A. Well, I was following Dr. Smith's reasoning, okay?
Q. Yes.
A. And what Dr. Smith reasoned was that the proportion of ANLL that was APL was 28.6. And he referenced the statement made by Travis where she said the proportion of ANLLs or APLs was similar to what we saw in the general population of China, and referenced the Yang paper. So I went back to the Yang

paper to see if, in fact, that was true and, in fact, we see -- or as we saw, the Yang paper said it was 18.7 percent. So I said, you know, that's a better -- that's a more reliable estimate than 28.6 as Dr. Smith used. So let's do Dr. Smith's calculations using the 18.7 percent, not the 28.6. So I did those calculations.

Q. Yes. And once you did those calculations that we're presently seeing for the first time, what you found -- let's just back up to say you described this as a more plausible assumption to do with respect to the Travis paper than what Dr. Smith did, correct?

A. Well --

Q. That's how you start this line.

A. The proportion of ANLL that was APL is -- the number 18.7 percent is more plausible than Dr. Smith's assumption of 28.6 based on a very small amount of data.

Q. So your answer is yes, correct?

A. Yes.

Q. And in connection, once you did this calculation to, quote/unquote, correct what Dr. Smith did, what you found was -- when you counted the APLs that the Travis 12 authors determined were APLs, when you counted those four, you had an observed of 5.98, an expected of 2.3, and a rate ratio of 2.6, correct?

A. Right. Now, let's walk through the calculations. All

right. So what this is about is saying, look, if we assume that 18.7 of the ANLLs were APL, and we follow Dr. Smith's method, which I don't think is reliable, we would estimate 5.98 cases of APL in the Travis cohort. I then said, now, let's try and figure out what the expected is, and I'll use Dr. Smith's estimates that range from three per million to eight per million -- eight per million per year -- so 380. That's a range he gave. That would generate expecteds in the range of 2.3 to 6.3. So these are boundary calculations.

So if you use the 5.98 observed -- or I should say there were four observed plus two created -- versus 2.3 expected, you get a rate ratio of 2.6 and a p-value that is not quite statistically significant. If you use Dr. Smith's other assumptions that the background rate is eight per million person years, you get 6.3 expected. Compare that to the 5.98 that you have calculated, now you have a rate ratio of 0.95; in other words, no association.

The point of these calculations is to indicate that, depending on what you assume, you might or might not get any association at all. Both of these are guesses. These are just guesses. And depending on what you guess at, you can find an association or no association.

Q. Well, now, let's back up because I want to get back to my question. You've just given an answer, but that wasn't my question. My question was: When you -- when there were four

APLs in the Travis paper, the amount of expecteds -- the amount of expecteds, the rate ratio would be 2.6, right? Am I right?

A. No, you're wrong.

Q. I'm wrong? Okay. The top number that we have here in this line, that rate ratio of 2.6, would you agree with me that if that assumption is a correct one -- and I understand you don't believe it's a correct one, but if that assumption is a correct one -- that that is a rate ratio that appears to be showing an association?

A. Which assumption?

Q. Line 1.

A. But which assumption is a correct one? There's a bunch of assumptions in there.

Q. Okay. Well, I'm not trying to play a word game with you. Line 1. Does line 1 where you have observed of 5.98, expected of 2.3, rate ratio of 2.6, that rate ratio -- would that rate ratio be showing an association?

A. By definition, a rate ratio of 2.6 is a positive association. It is based on three assumptions that are questionable.

Q. Well, when you worked this math, this was what you laid out in a slide as more plausible assumptions, correct?

A. No. This is what I laid out in a slide to show that depending on what you assume, you can get answers that range from no association to a 2.6-fold association. That's the

point of the slide.
Q. I understand. In fact, the slide starts, "It is possible to make other more plausible assumptions about the number of cases of APL in the Travis cohort," correct? That's what you wrote?
A. That's what I wrote. And I meant "more plausible than what Dr. Smith presented."
Q. Uh-huh. And when you made those more plausible assumptions -- when you put together the more plausible assumptions based on your understanding, and you got to do the math -- in the first category you found a rate ratio that would show a positive association, correct?
A. Yes. More plausible than what I regard as an implausible assumption made by Dr. Smith; however, the bottom line on this slide is still the correct one.
Q. Okay. Well --
A. If you make a bunch of guesses, you can come up with widely varying results. That's it.
Q. Well, Doctor, that might be what you want to say that it's about, this slide, but I'm entitled to talk about what I want to talk about on this slide, and I want to talk about the p-value with respect to that rate ratio. Because on that p-value with respect to that rate ratio, what that p-value is telling us is that number, that rate ratio, 2.6, is a p-value that shows 92 percent confidence, correct?

A. That's not what it means.
Q. Oh, doesn't it mean that there's an 8 percent chance that that -- that there's an 8 percent likelihood that that number's due to chance?
A. Okay. Let's go back to what p-values mean.
Q. Is that a yes or no? And then you can explain your answer.
A. That's a no.
Q. Okay.
A. Okay? What the p-value is is the probability that you could have gotten the data you got by chance alone when there is no association whatsoever in the data. Now, what the p-value doesn't do -- and of course this really goes back to Austin Bradford Hill -- is it doesn't tell you anything about the reliability of the data. So where we've created data that really don't have any reliability and then make calculations of p-values, the p-value doesn't in any way fix the unreliability of the data; it just says that if there were really no association -- and you assume the data was reliable -- this is the probability that you could have gotten these data by chance alone when there was no association to the data.
Q. Okay. So let's get back to the p-value. And I understand that you don't like the data points that you put in here, correct?
MR. LEGHORN: Objection to the form, your Honor.

Argumentative.

THE COURT: No, go ahead.

BY MR. STEWART:

Q. Am I correct?

A. As I've said now repeatedly, the assumptions that created these data I think are not reliable.

Q. Uh-huh. I understand.

A. Okay? So what that means is that the data have no particular reliability.

Q. Okay. And so my question was: You don't like the data points that you put in. Yes?

A. Well, I think I've answered it.

Q. Okay. Well, just for the sake of time, I'm really trying to ask you yes-or-no questions. So --

A. And, sir, I'm doing my best to answer them correctly.

Q. Okay.

A. They don't reduce to yes and no so simply.

Q. I'll do my best to keep asking them as most of the time we can get yes and noes if we try.

Now, let's go to the next issue, which is the p-value component that we have here on Line No. 1. What you're saying is that that p-value of 0.08 doesn't have any meaning because you don't like the inputs into the system, true?

A. This is an example of garbage in, garbage out, okay? If you put garbage numbers in, you can create p-values that are

very small. Okay? That's what it is. The p-value's just a calculation; it doesn't comment on the validity of the data. It's just a calculation. And, yes, it's 0.08.

Q. Okay. And you've made the decision that it's garbage you're putting in so that you can now come testify that you just think this calculation is garbage coming out, right?

A. The point of the slide is that if you make assumptions about what the data ought to be and change the data, you can get different answers. That's it.

Q. I wasn't asking about the slide, sir.

A. Okay.

Q. My question didn't have anything to do with the slide. My question really was really simply: You have come to say "I've made the decision that this is garbage in," so that you can come into the courtroom and say, "and now this is garbage out," right?

A. No. I've tried to use accepted methods that are widely applied in epidemiology to try to make reasonable inferences from the Travis data. I've also tried to follow Dr. Smith's reasoning and to show that, depending on what Dr. Smith assumes, you can find or not find an association. And, yes, you can calculate p-values and confidence intervals. And there they are.

Q. Thank you. Because one of your criticisms of Dr. Smith was that he didn't calculate p-values, right?

A. Yes. Dr. Smith made no attempt to assess the role of chance in his results.
Q. Yes. And so what you have done is you've crunched some numbers that were Dr. Smith's numbers, yes?
A. Well, they are based on Dr. Smith's assumptions, yes.
Q. That's fair. And once you crunched those numbers based on Dr. Smith's assumptions, you then -- after doing that, you crunched some more numbers with a more plausible assumption made by you which would reduce the numbers, correct?
A. Which are you referring to --
Q. I'm referring to your 18.7 percent of ANLL was APL as observed in Yang.
A. Well, that was actually the number that Travis referred to.
Q. I'm not quarrelling with you. What I'm saying is you quarrelled with Dr. Smith using a number different than 18.7 percent, correct, in his calculation, all right?
A. Yes. I said that had no basis.
Q. Yes. So what you did was you threw out the number that Dr. Smith used and you inserted the number 18.7 percent, correct?
A. Based on a published paper by Yang, yes.
Q. Okay. And once you did that, now what you're doing is you were working on correcting, with your logic, Dr. Smith's calculation, correct?

A. Based on Dr. Smith's logic and still allowing some of Dr. Smith's other assumptions. So, again, what I'm doing is looking at the effect of his assumptions on the results. And so you can do that for a number of different assumptions and work through. It's sort of a sensitivity analysis. If you question this assumption, you put in something different, what happens? Question this assumption, do something different, what happens? Yes, I did that.

Q. Yes. And so these numbers that we are seeing here that are calculated on the screen are you putting in corrections to Dr. Smith's assumptions, right?

A. No. I'm doing what I would say is a sensitivity analysis and showing how sensitive his results are to changing his assumptions one at a time. So if you change his assumption about the proportion of ANLL that was M3, here's what happens. If you change his assumption about the background rate, here's what happens.

Q. Yes. And I'm trying to make this easy. You made corrections to what Dr. Smith's assumptions were and generated these numbers, right?

A. Well, I think I've answered that. I have -- I wouldn't say I've made corrections. I've showed that the effect of changing the assumptions has dramatic effects on the results; that's all.

Q. Yes. Now, I'm back to line 1. When we insert the

correction to -- your correction to Dr. Smith's assumption of 28-some-odd percent of AMLs had APL, and when we insert what you think is a more plausible assumption -- let's use Yang. When you do that, when you put in the 18.7 percent number, you still get a rate ratio of 2.6, right?

A. Yes.

Q. You still get a positive association, right?

A. Okay. But here's the point: I don't believe any of this has validity. This is a bunch of guesses.

Q. Okay. But wait a second.

A. And the guesses -- and the results are very sensitive to which combination of guesses you use. And you can find a set of guesses that will give you a rate ratio of 2.6 that has borderline significance. You can find a set of guesses that will do that, okay?

Q. Okay. Dr. Garabrant, respectfully, you've now told me that theory three or four times. I'm asking very discrete questions about what this shows, not how you interpret it. Just that 2.6 is a positive association, right?

A. Yes, by definition.

Q. Yes. Now I want to get to the p-value on that 2.6. And once you've made your correction to Dr. Smith's assumptions and you generated this p-value, that p-value of 0.08 that you're showing there, that is not an insignificant p-value, is it?

A. Well, there is a convention that P less than .05 is

statistically significant. If you want to change that, okay.
Q. Well, I'm not saying I do want to change that. I'm pointing out you've said earlier that while that's a convention, other people can disagree with it, right?
A. I suppose there are people who disagree with that, but it is a convention that's widely followed.
Q. Yes. And in that convention -- so a .05 p-value in that convention, what you're saying is there is a 95 percent probability that the result is not due to chance, correct?
A. You know, we use the words very carefully, and I have to think whether what you've said is correct mathematically. Let me say the correct conclusion. When you have a p-value of .05, it says there is a 5 percent probability that you could have gotten these data, all right? It's not about the rate ratio; it's about the data. You could have gotten these data by chance alone when the truth is that there's no association at all. And then the calculation of the rate ratio follows from the data. That's what the p-value means.
Now, what you've said is the -- what -- the inverse of that, there's a 95 percent chance that it's not due to chance. And I don't know whether that's right or not. But let's just leave it the way we say it. When you have a p-value of .05, there's a 5 percent chance that you could have gotten data such as this by chance alone when there's really no association. But, again, you have to note that there's nothing in the

calculation of p-values that comments on whether the data are valid; in fact, you shouldn't calculate p-values from invalid data. You shouldn't do it when you've got a biased set of data. It's wrong to do so.

Q. Well, you're the one who did it, right?

A. For the purpose of showing that Dr. Smith's various assumptions and alternatives to those assumptions give wildly different answers; that's all.

Q. Let's go back to the p-value and let's use your definition. This means that your calculated p-value there, there's an 8 percent -- based on the p-value there's an 8 percent chance that you could come to that data by chance alone, right?

A. When there is, in fact, no association at all.

Q. Uh-huh.

A. You have to put that part of the definition in as well.

Q. That's fair. And in that first line it's showing a positive association, right?

A. I've answered that, yes.

Q. Okay. Now, you said, I believe, that on your chart for the Bradford Hill considerations, that there was absolutely no association. "Strength of association." And you said, "How large is the effect?" And you said none, right?

A. When we look across the studies, okay, when we looked at Yang, there was no association. After Yang did his

multi-varied analysis and controlled further factors in the model, we didn't see an association. When we looked at Rinsky, we saw not a single case of APL recorded. Now, I'll agree with you it's possible that what was recorded didn't capture something that was known, but there's no evidence it was known. You have to go with what you've got. So we've got studies that have looked -- and these were benzene-exposed studies, okay?

Q. I'm sorry. I just want to interrupt. Why are you saying that the Rinsky study looked for APL when you've just admitted that the Rinsky study didn't look for APL? Nobody knows how many APLs were in the Rinsky study.

A. No. Excuse me. That's not true. If there had been a case of APL recorded on the death certificate, the Rinsky study would have shown it. And as you saw from those death certificates, there were very specific diagnoses listed for many of those cases. You know, you see DiGuglielmo's acute myelocytic leukemia. That is a specific FAB subtype. So for some of them, it was quite clear that there were specific types of AML recorded. There was no APL recorded. Now, I agree with you it's possible there was an APL that was recorded as an AML, okay? The point is there's no data in Rinsky that says there's an APL.

Q. Uh-huh. Okay.

A. Okay. So and --

Q. I want to go back to your statement of none -- that

there's none. No data. But this right here is some data, isn't it?

A. No. These are guesses. These are just guesses. The data in Travis does not show any association between benzene exposure and APL.

Q. Wait a second. You said these are guesses and yet you told me that what these calculations are, are your corrections of Dr. Smith's assumptions by using data, right?

A. No. I said these are -- this is a sensitivity analysis where if you changed Dr. Smith's assumptions, you can show that the results change dramatically.

Q. Okay. But you changed his assumptions to your liking, correct?

A. I changed -- I changed the assumption about the proportion of ANLL that was APL based on the Yang paper which was, in fact, the source of Dr. Travis's claim that the proportion was similar in the general population which was, in fact, the source of Dr. Smith's idea that you could use the proportions somehow.

Q. Yes. And when you put in these assumptions, these corrections to the assumptions based on data, these are the numbers you got, right?

A. I would say it slightly differently. When I made different assumptions, I got different results.

Q. Yes. And these were -- what you did was you made more

conservative assumptions than what you think Dr. Smith made, right?

A. I made assumptions that had a little better foundation in data than Dr. Smith's did.

Q. And you would agree, I think, that by picking these numbers, which you say are grounded in data, that these numbers end up creating a scenario where the rate ratio is lower than what Dr. Smith would have gotten, true?

A. Well, all right. Yes. Let's back up. These rate ratios are based on at least three assumptions by Dr. Smith which I think cumulatively lead to a wrong answer.

Q. I understand that, Dr. Garabrant. You've made it clear you think Dr. Smith is wrong, okay? And what I'm trying to point out is, by then putting in corrections to make Dr. Smith more right, you are still getting a rate ratio that's 2.6 in one instance, correct?

A. You've misrepresented what I've said.

Q. I haven't. I haven't tried to, anyway. That's what your first line -- your first line has "Corrections to Dr. Smith's assumptions" using, in your words, "data."

A. The last sentence in bold. The point is that Dr. Smith's guesses, his assumptions, are no better than other guesses. The results obtained for guessing can be anything you want them to be. You can make a set of assumptions that yield associations, but the association is just based on the

assumptions you make. If the assumptions are wrong, the association has no meaning. It's not reliable. That's the point.

Q. So, Dr. Garabrant, what you've really come to do here is to say that you don't like the assumptions that Dr. Smith has made, correct?

A. Well, having 30 years of experience as an occupational epidemiologist and designing these studies and collecting the data and analyzing the data and publishing the papers, I have some experience in what are reasonable assumptions and reasonable methods for calculating things. It is my opinion that what he's done is not reliable.

Q. Yes. And as a matter of fact, this is what you routinely do over the last four years: You come into courtrooms and you sit up on the stand, or in depositions, and you say about other scientists, what they have done is unreliable. That's what you do, right?

A. Only when it's unreliable.

Q. Well, you do it to the tune of more than a million dollars over the last four years, right?

A. Only when it's unreliable.

Q. Hmm. That's a lot of unreliability, isn't it?

A. There are things that are done that I think don't withstand scrutiny.

Q. Well, sir, when you get involved in cases there are very

few things that withstand your scrutiny; isn't that true?
A. No, sir.
Q. So can you point to me on this list of these cases, 62 cases, where you said that you thought that the expert for the plaintiff had been reasonable and reliable in their opinion?
A. Well, I'd have to see the list. I can't do it from memory, and to be honest, I'm not sure I recall everything that was said in every one of these cases. Sure.

Karen Brown versus Christus Spohn Health System. This is a lady who got a barium enema and they perforated her colon. I felt there was no question they had perforated her colon. I agreed with the plaintiff. The question was whether she had barium poisoning. I felt she did not have barium poisoning. She got peritonitis from the barium preparation, the contrast agent. So I agreed they perforated her colon, I agreed they pumped a whole bunch of barium material into her peritoneum, and I agreed she got peritonitis and she was disabled as a result of that.

The one issue that I disagreed was she didn't have barium toxicity; she did not have any specific toxicity from barium. But other than that, yeah, I agreed with the plaintiff.
Q. Okay. So you disagreed with the plaintiff on the central point in the case, which was barium poisoning, right?
A. No, I don't think it was the central point. I think the central point was that a mistake had occurred and she had been

damaged by it. And it was a peripheral point as to whether she had barium poisoning. She did not have barium poisoning.

Q. The only reason I'm asking for this back, it's the only one I've got.

THE COURT: Are you going to turn to something new? We'll take the morning recess.

MR. STEWART: That will be great.

THE CLERK: All rise.

The Court will take the morning recess.

(There is a recess in the proceedings from 11:07 a.m. to 11:30 a.m.)

THE CLERK: All rise.

Resuming the Milward Daubert hearing.

Please be seated.

MR. STEWART: Thank you, your Honor.

BY MR. STEWART:

Q. So, Dr. Garabrant, I want to talk about two more issues. I had more, but I cut them down at the break. We need to get you off the stand and get things done.

The next issue I want to talk about is I want to talk about the Mele study called "Epidemiology of Acute Promyelocytic Leukemia" which you talked about a little bit on direct. And you would agree that in this study in 1995 there was a strong association between shoemakers and APL in Italy, true?

A. Yes.
Q. Yes. And you would also agree that these authors, in their discussion section in connection with that, said the following: "The significant relationship between shoemaking and APL is possibly related to benzene exposure, a well-known leukemogenic agent present in the glues," correct?
A. Yes.
Q. Okay. Now, these are the same authors that you cited from an earlier paper that showed that the benzene content that was supposed to be in the glues after 1963 in Italy was not supposed to be any more than 2 percent, correct?
A. They said whatever I showed they said, that -- I think it was that the content -- it said in Italy the use of glues with the benzene content greater than 2 percent was prohibited by law in 1963.
Q. Yes. And what that statement means is that it would have been illegal to use glues that had more than 2 percent in Italy, correct?
A. Yes.
Q. All right. But the statement also means that glues in Italy after 1963 could still have benzene in them, right?
A. As far as I know, the law restricted it to 2 percent.
Q. Which means the law allowed up to 2 percent benzene in the products, right?
A. As far as I know.

Q. And, sir, that's something these authors in 1995 -- these Mele authors knew when they wrote the sentence that "The significant relationship between shoemaking and APL is possibly related to benzene exposure, a well-known leukemogenic agent present in the glues," right?
A. I assume they knew it. They had written the other paper the year before.
Q. Yes. And, sir, this is a reasonable statement by original researchers about their topic, what they had researched, and what their possible conclusions could be from that research, true?
A. Well, it's as they said, it's possible, or possibly related. It's important to recognize the Mele study had no measurements of benzene exposure. They had no documentation of benzene exposure. They reported an association between APL and working as a shoemaker. That's it.
Q. Well, that's not all they said. They then reached the conclusion that this could possibly be related to benzene because it's a logical connection that benzene is used in shoemaking work, true?
A. Well, they said it's possibly related. Okay.
Q. That's a reasonable conclusion from their research, right?
A. I think it's exactly what they said. It's a possibility. That's it.
Q. Do you consider that a reasonable statement?

A. That it's a possibility? I think based on what we know at the present time, which is now, what, 14 years after this was published, that possibility has gotten a little smaller.
Q. So what I would like to do is I want to put your Hill considerations list back up on the screen here. And this is going to be the last thing that I do. You went through these factors, the Hill considerations. And this is what I want to ask you: With respect to these factors, Number 1, there is a significant strength of association for benzene causing AMLs generally, true?
A. I believe -- well, I don't know what you mean "there's a significant strength of association." I believe it is well established that benzene can cause AML under circumstances of high exposure. And I can give you the full definition of my view on that. But benzene can cause AML.
Q. And you would agree that, with respect to Number 2, consistency of association, there is ample evidence of a consistency of association of benzene causing AMLs generally, true?
A. I believe there is an adequate body of knowledge to adequately support that conclusion. It's not perfectly consistent; there are some studies that show variation. But I would say, yeah, there's enough consistent evidence that supports it.
Q. Yes. Number 3: Is there enough evidence to support

specificity in Number 3 for the proposition that benzene causes AMLs similarly?

A. I think that there is adequate evidence -- you know, "specificity" has two elements. Is the exposure specific? Is the outcome specific? What we know, in my opinion, clearly is that benzene specifically is linked to AML whereas related materials such as toluene, xylene, petroleum distillates, gasoline have not been related to AML. So when you get to the specificity, you get to the benzene, yes, on that side.

On the AML side, when you group all AMLs together, there's clearly evidence of an association. But it is not clear that each and every type of AML. So that's, of course, the issue today. It is not clear that APL, specifically, is related to benzene. In fact, we're looking at the evidence today. That's what we're doing.

Q. Okay. So, Dr. Garabrant, for the sake of time, please, I'm keeping my question specifically to AMLs generally and benzene, all right? That's my question.

And with respect to Number 4 -- you adequately answered Number 3. Number 4, temporal relationship, you'll agree that there are studies out there that show benzene exposure first, AMLs afterwards, right?

A. Yes.

Q. All right. Now, Number 5, biological gradient. You will agree that there's ample evidence of a dose-response curve for

benzene exposure and AMLs generally, true?
A. Yes.
Q. Number 6: Plausibility. You would agree that there's ample evidence of the biological plausibility of benzene causing AMLs generally, true?
A. You know, that's actually a harder issue. To the extent I understand the biology, it took many, many years to come up with an animal model that would support that -- the association seen in humans. And the mechanism by which benzene causes AML still has some elements that are not clear. So that one's not a yes/no answer. But largely I would say yes, for benzene and AML as a group of diagnoses, the plausibility is reasonable.
Q. Okay. Coherence: You would agree that the coherence with benzene and AMLs generally, that that is satisfied, those considerations?
A. Yeah. It doesn't conflict with any generally known facts about the natural history and biology of AML. In general, again, not looking at APL specifically.
Q. Now, with respect to experiments, you would agree there is ample experimental evidence that preventative action does, in fact, prevent AMLs generally?
A. No, I don't think there's any experimental evidence. What Hill is talking about is instituting some control. And he was actually talking about the cotton industry where, when they controlled exposure, they were actually able to reduce the

incidence of byssinosis.

No, I don't think there's any experimental evidence where we can show that reducing benzene exposures has prevented the disease. I don't think it's there.

Q. Oh, okay. And I understand your distinction. I was actually thinking about studies of industries that had large benzene exposures, and when those benzene exposures were eliminated, the rates of AMLs generally went down.

A. I'm not aware of any such study that has shown that.

Q. If you don't know, that's fine.

Number 9: Analogy. Do you believe that the analogy consideration is satisfied in benzene causing AMLs generally?

A. No, there's no analogy. There's no other compound like benzene that causes AML.

Q. Okay. So what I hear you saying is even though Number 8, you're not aware of; Number 9, by analogy you're not aware of; Number 6, there's not really a yes or no on plausibility, that's still with respect to benzene causing AML generally, that the Hill considerations that it does satisfy are such that you believe benzene causes AMLs in humans --

A. Yes.

Q. -- with sufficient --

A. Yes. With sufficient exposure, with the right timing, yes, I do.

Q. All right. I think that's all the questions that I have,

Doctor, at this time.

MR. LEGHORN: Your Honor, just a brief redirect?

REDIRECT EXAMINATION

BY MR. LEGHORN:

Q. Dr. Garabrant, while I get set up, you talked about sensitivity testing. What do you mean by that?

A. Well, what I was doing with the various calculations is assessing how sensitive the association in the Travis study was to different assumptions made by Dr. Smith. And he made a bunch of assumptions in doing his calculations. And so I was testing different assumptions and seeing what the effect was.

MR. LEGHORN: Your Honor, I'm going to use this to make it work, not in the full-screen mode --

THE COURT: All right.

MR. LEGHORN: -- because I may be flipping back and forth. I just want to warn the Court about that.

BY MR. LEGHORN:

Q. This was the slide -- and I'll try to make it as big as I can here --

A. Put it on the slide-show version.

Q. I don't want to because when we flip back and forth...

A. Okay.

Q. And one of the things, Doctor, here is you said there were a number of assumptions there, correct?

A. Yes.

Q. And here the issue -- can you tell us, in the "observed," what were the assumptions that you were making to come up with that number?

A. Okay. Well, the first assumption is that it's even meaningful to infer that there were cases of APL where Travis and colleagues didn't find them. And that's a very strong assumption -- I should say that's a very questionable assumption, that you can do that. I don't think you can; I don't think you should. But that was Dr. Smith's method.

So I said, all right. We'll allow the idea that you can create cases where none exist, and so let's use Yang's evidence of the proportion rather than Smith's assumption of a proportion.

Q. And when you're talking about creating cases, that's what was displayed on this slide here; is that correct?

A. Yes.

Q. That we now see the one where you have the red arrows and where under the total cases 9.2 apply, right?

A. Yes. Travis reported four cases of APL. Dr. Smith's method creates five additional cases that were not diagnosed.

Q. And so when you did the sensitivity testing you, in fact, in the -- created an additional two cases?

A. So I said if you change the proportions from Smith's assumption of .286 to Yang's reported .1 -- I can't remember it. I apologize -- to Yang's reported 18.7 percent, this is

the effect of changing that assumption -- you get 5.98 observed. So you've invented two cases instead of 5.2.

Q. And to do this you used Dr. Smith's estimate of three to eight cases per million; is that correct?

A. Okay. Here I am using, in order to calculate the expected number of cases, Dr. Smith's testimony that the background rate is somewhere between three and eight cases per million, which yields expected numbers of 2.3 to 6.3.

Q. And that's three times .187 and eight times -- you adjust --

A. No. No. No. No. No. No. That's using Smith's estimate of background rate, okay, three per million person years or eight per million person years multiplied by the roughly 750,000 person years at risk in the benzene cohort.

Q. And then when you did the calculation that you showed in your direct testimony using information from the Zhang study here, you were using the four actual cases reported as APL by the 12 doctors in the Travis study, correct?

A. Okay. This slide shows, yes, the four observed by Travis that they felt existed. Right, that's the four observed.

Q. And in the other slide, just to make sure that we're clear, you're doing the Smith technique of generating extra cases?

A. Yes. Generating an extra 1.98 cases using Dr. Smith's method.

Q. And in the field of epidemiology, can you tell us whether generating additional cases where the diagnosis is unknown is an accepted method?

A. I've never seen that done. Not to my memory, no.

MR. LEGHORN: No further questions, your Honor.

MR. STEWART: I don't want to do any more math.

THE COURT: All right, sir. Thank you. You may step down.

(The witness is excused.)

MR. WEATHERS: Your Honor, the defense calls Dr. John Bennett. And as Dr. Bennett is making his way to the witness box, the time issue: Is there a chance of us extending a bit today, if we need to, beyond one?

THE COURT: It depends on what you mean by "a bit." A bit, yes; a bunch, no.

MR. WEATHERS: So we don't have an hour more; we have minutes more?

THE COURT: No.

MR. WEATHERS: All right. We will do our very best, your Honor.

And in that regard, there are two papers that I believe have not been previously identified in this proceeding. I would like to hand those up to the Court. I'm providing a copy to Dr. Bennett and a copy to counsel.

JOHN M. BENNETT, sworn

THE CLERK: State your name, spell your last name for the reporter, keep your voice up, and speak into the mic.

THE WITNESS: I'm John M. Bennett, B-E-N-N-E-T-T, 601 Elmwood Ave., Rochester, New York 14642.

DIRECT EXAMINATION

BY MR. WEATHERS:

Q. What's your current position, Dr. Bennett?

A. I am professor emeritus in Laboratory Medicine and Pathology at the University of Rochester, and currently in active practice of hematopathology.

Q. Doctor, the Court -- Judge O'Toole has your report, will have your CV. And in the interest of time, if you will allow me, sir, I'm going to summarize a bit of your considerable background. Is that fine?

A. That's fine.

Q. Doctor, you graduated from Harvard College, cum laude; you graduated from Boston Medical College, from Boston University College of Medicine, cum laude; took an internal medicine rotation at Boston University Medical Center and a hematology fellowship at Boston City Hospital, correct?

A. Correct.

Q. And you then had some experience with the U.S. Public Health Service, correct?

A. Yes. Before that I was a staff hematologist at the Beth Israel Hospital in Boston and in charge of the Hematology

Diagnostic Laboratories from 1963 until 1966.
Q. And then later you had some involvement with Tufts Medical School where you taught, and with an outpatient hematology lab at Boston City, correct?
A. That's correct.
Q. Tell us just briefly, Doctor, have you had involvement on advisory commissions or editorial boards prior to the time that you became an emeritus professor?
A. Oh, yes. Extensively.
Q. Give us examples.
A. I've served as chairman of an NIH advisory board on chemotherapy in a variety of different cancers sponsored by the National Cancer Institute; I serve currently as chairman of the Scientific Advisory Committee of BioReference Laboratories; chairman of the Myelodysplastic Syndrome Foundation; and also editor-in-chief of the International Journal of Leukemia Research, which is one of the articles you heard about this morning.
Q. What did you do professionally, Doctor, prior to the time that you became -- that you took emeritus status?
A. I served as clinical director of the cancer center at the University of Rochester and saw many patients, primarily with hematologic diseases, and also served as a pathologist of reference for the Eastern Cooperative Oncology Group looking at anywhere from six to seven hundred cases a year of acute and

chronic leukemias.
Q. Doctor, during that time period, so we're all clear, did you actually diagnose and treat leukemia patients?
A. Oh, yes.
Q. Was that a major portion of your professional life?
A. It was a majority of what I did.
Q. Post-emeritus -- after you took emeritus status -- tell us about your professional practice in summary, please.
A. I serve as a consultant to the medical staff of the cancer center, and then one week a month actually sign out all the bone marrows and peripheral blood smears of patients who had marrows performed looking for a diagnosis. So it's a formal sign-out.
Q. And, Doctor, is that only cases referred from within your institution?
A. About 85 percent from my own institution, 15 percent from other institutions.
Q. Doctor, in testimony -- first of all, you were not here with us Tuesday, correct? You were not present in the courtroom?
A. That's correct.
Q. But you have subsequently had an opportunity to read Dr. Smith's testimony; is that correct?
A. That's correct.
Q. All right. And, Doctor, I think that Dr. Smith's made

some comment about he wasn't sure whether you had done any research regarding causation of disease. I would ask you that question, sir: Have you?

A. Yes. In addition to a series of publications on diagnosis as well as management of leukemias, I have participated in at least a half a dozen epidemiologic studies looking at causation of a variety of different agents including cancer chemotherapy drugs, ionizing radiation that occurred in Japan after the detonation of the two atomic bombs, and at least one study on potential benzene exposure in a prospective study for the Shell Oil Company.

Q. All right. Doctor, to this point we've all heard a great deal about the -- what's called the FABs. I'm sorry. I apologize. We apparently don't have that slide. But --

A. It's disappeared.

Q. It seems to have. But nonetheless, what I was going to put up was a list of all of the FABs, correct?

A. Right. And I founded the French-American-British working leukemia group in the early 1970s. And over the past 35 years we have produced approximately 15 papers codifying the various types of both acute and chronic leukemias. And they're referred to as the FAB classification.

Q. So, Doctor, when we talk about the French-American-British system of hematological identification, would it be fair to say that you were the American portion of that?

A. I and one other investigator from the National Institute of Health, Dr. Harvey Gralnick. The two of us. There were seven members of the group.
Q. And when was that, approximately, Doctor?
A. The first meeting occurred in 1972; the first publication in 1976; and there have been a series of publications including the most recent one in January of this past year.
Q. Now, Doctor, we've also heard a good deal about the WHO, the World Health Organization, and the ICDs. Are you familiar with those?
A. Yes, I am.
Q. And have you had any involvement with those directly at --
A. Yes. I was one of the original members that put together the chapters for both the acute and -- acute leukemias and the myeloplastic syndromes, the first edition that was produced ten years ago and the more recent update that was just released last year.
Q. Doctor, the defense asked you to serve as an expert witness in this case and to consider whether there is reliable science to connect or associate the disease, acute promyelocytic leukemia, with exposure to benzene. And have you reached an opinion on that question, Doctor?
A. Yes, I have.
Q. And what did you do to inform yourself prior to reaching that opinion?

A. Well, based on my experience as a hematopathologist and diagnosing and managing cases, serving as an inpatient director of the leukemia service for many years, talking with patients and then reviewing the literature, much of which you have heard already over the past two days.

Q. All right. And, Doctor, what was your opinion after reviewing those sources and obviously bringing to bear your considerable background?

A. That there is no reliable evidence to support a linkage between benzene exposure and APL.

Q. Doctor, I'm going to generally characterize that one of the principal predicates of Dr. Smith's testimony was that benzene causes AML, and APL is one of the -- APL is one of the AMLs. Now, Doctor, my question is in that regard: Do you have an opinion as to whether APL, acute promyelocytic leukemia, is a unique and distinct disease?

A. Yes, I believe it is.

Q. And we have now a slide in front of us. Can you refer to that and give the Court your basis for that conclusion?

A. So of all of the leukemias we see, acute promyelocytic leukemia has a very unique morphology. By that we mean what the cells look like under the microscope. It has very unique chromosome abnormalities. And then there are a series of other steps that I'll come back to.

So that if we could go to the next slide.

Q. Is this it?
A. Yeah. I can't read...
Q. I'm sorry. It's too dark?
A. Well, it's not the font that we originally had which is -- I don't know how it shows up.
Q. It shows up fine on my --
A. Okay. I -- it's showing up as black on my monitor.
Q. So you can't read it?
A. Well, I can -- yeah, I guess I can read it. All right.

So, your Honor, what I've tried to do here is to define the various types that are commonly called APL. And as you can see, over on the right-hand side I've listed the approximate percentages, as though we were dealing with 100 consecutive cases, of all of these different cases of APL. Obviously, the most common type is what we call hypergranular APL that has the 15;17 translocation, and the rearrangement between the PML and the RAR-alpha gene. And that constitutes about 83 percent.

Then there is what we call the microgranular variant. And we've used that term back in the early '80s to describe about 15 percent of patients who, for reasons that we still do not understand, have a different morphology of most of their cells. Occasionally you'll see the classical cell, but you really need to have the chromosome information to be sure you're dealing with APL. It has the same genetic rearrangements; its biologic behavior is the same as far as its responsiveness to

chemotherapy and all-trans retinoic acid, which has become the hallmark of the treatment success of this disease.

Thank you.

(Laughter.)

THE WITNESS: I thought maybe it was my glasses.

So now we're down to two. And the problem in the terminology is that we describe what we call M3v the variant, which was agranular or hypogranular. I'll illustrate that in a moment. But then others have said, yes, but there are some variant translocations. And they're, then, characterized by A, B and C. And these represent a trivial percentage of the cases we see. And we believe on morphologic grounds that we can separate these out pretty well, and we have so published in Leukemia on that.

All of these variants involve Chromosome 17. Every one. But they have a different part of the chromosome. One has -- and there are two, interestingly enough, that are both 11;17s, but the breakpoints on the long arm of the chromosome is at a different site; and, therefore, you get a different rearrangement of the gene products. But they all have an RAR-alpha, but they are different genes that are defined there for you. The importance of this is that when you recognize this, these patients do not respond as well to combination chemotherapy with all-trans retinoic acid.

And then very recently -- and Dr. Smith referred to

this in his testimony two days ago -- two pediatric cases of an unusual 5;17 -- so that's Chromosome 5 hooked the Chromosome 17, so they formed a fusion chromosome -- have been described that has yet another part of the gene -- and this does not respond to all-trans retinoid acid that we call ATRA, either. So that basically defines APL in all of its variants in sort of a word fashion.

Now, if we can go back. So we've now covered Points 1 and 2. Points 3 and 4 I'll come back to.

Characteristic immunologic phenotype was referred to earlier. This means that there are proteins on the cell membranes of all of these cells which we can identify with antibodies. So we purchase these antibodies, we attach them to a chromophobe, which is a fluorinated colored compound, and we flow them in a machine that flows literally millions of cells, sorts them out by the type of protein that is present on the cell membrane. And we have published on this. We can come up with a characteristic phenotype of APL that is present in about 92 percent of the cases. It can be seen rarely in some other patients with different types of leukemia. And I've just listed here for you three of the antigens that we see characteristically: CD33; '13; and HLA-DR, which is on the minus side, is not present.

Now, '33 characterizes a cell that has gone one step beyond a stem cell. So you have to keep in mind when we talk

about stem cells, we're talking about at least a cell that has CD34 on its membrane, and the vast majority of patients with APL do not have CD34. So try to remember that.

High curability with chemotherapy and ATRA: For classical APL we currently are curing 85 percent of all patients, pediatric as well as adults, which has been a major achievement over the past decade. So it is the most curable of all of the acute leukemias that we see in adults, whether it's acute lymphocytic leukemia or acute myeloid leukemia.

Now we can go to the pictures.

All right. So this is an example of a classical case of acute myeloid leukemia. And it's acute myelogenous leukemia. And if you look at the lower right, the second cell up in the cytoplasm -- now, think about a fried egg, okay? The yellow part of the egg is the nucleus, and the white part of the egg is the cytoplasm. So in all of these cells the nucleus is purple and the lighter color is the cytoplasm.

And in that cell, on the lower right you'll see a little small rod-like structure that is colored pink. That is called an Auer, A-U-E-R, and was defined by Dr. Auer almost 100 years ago. It is a classical defining feature of acute myeloid leukemia. We can see cases of AML without it, but when we see that particular cell, you know you're dealing with acute myeloid leukemia.

This particular case -- and you have to take my word

for this -- comes from a patient who has an 8;21 translocation, one of the specific translocations which is highly curable as well in AML, but the cure rate is closer to 60 percent rather than 85 percent.

So if we go to the next slide, this is APL, classical hypergranular APL. Why hypergranular? If you look where the white should have been, it's now replaced by innumerable pinkish granules and darker rod-like structures. And if you look at the upper right, below the red cells you'll see a little piece of cytoplasm has split off the cell and has a little rod-like structure in it.

Now, this is what happens: These cells self-destruct. They circulate in the bloodstream. They release an enzyme that converts fibrinogen to fibrin. And if you don't treat these patients quickly and promptly, they will bleed out. So this is an example of a case of hypogranular promyelocytic leukemia, and these granules contain proteins that trigger the coagulation system to clot. And it will clot, and you will lose all your clotting factors, and patients bleed out. They have brain hemorrhages or pulmonary hemorrhages. So very -- treatment is required instantaneously.

Thank you. That's perfect. Next?

All right. Now, this is an example of an agranular, or microgranular, variant. And it looks totally different. There are very few cells with granules, and instead you see

this doubling of the nucleus. A very characteristic feature. Now, occasionally this can be confused with another variety of acute leukemia that we call acute myelocytic leukemia. And, again, experts in this field of hematopathology, obviously experts, are able to pretty well look at this and say, "I strongly suspect this is APL, but let's wait until we get back the flow and wait until we get the cytogenetics." With a case like this we would institute therapy on a morphology without waiting for anything else to come back.

Now, in the Travis paper, Dr. Garabrant was concerned about one case that was called microgranular because it didn't fulfill the usual criteria that we expect to see in a patient with APL, which is a very high white count and a lot of circulating blasts, well above the 20 percent that that particular case had.

I think we can go back. Okay, we can go forward. We can go back one.

BY MR. WEATHERS:

Q. You said you were going to come back to bullet points --

A. Okay. So we're going to discuss a couple of papers that address Bullet Points 3 and 4. We've now -- and I don't think that that -- the other translocation slide helps very much.

All right. So about a decade ago a paper appeared in the journal of Blood. Number one, what does that mean? Well, Blood is believed to be -- and I think everyone would probably

agree -- the number one hematology journal in the world. They accept no more than one out of ten papers that they receive. So there's a very high rejection rate, which means that they are selecting only the very best papers. They also have reviewers who are the best reviewers in the country. So I'm editor-in-chief of Leukemia Research. We reject 60 percent of our papers. So we're not ranked quite as high.

So ranking, what we call "impact factor" which is calculated by an international agency that looks at how often a paper is quoted by someone else, turns out to be an important mechanism of where people send papers. You don't want to send a paper to a junk journal even though they might publish it. So you try to send your papers to the very best journals. Leukemia Research ranks in the top 25. Leukemia ranks about 20th; we rank about 25th; Blood ranks number one. So that's just sort of background.

MR. WEATHERS: To clarify one other thing, your Honor, that's the Turhan paper that we just handed up.

THE WITNESS: So this paper has four, five, six, seven -- nine authors. All of these authors are from the same institution in Paris. The hematopathologist in that hospital is one -- when that was written; he's subsequently retired -- was one of the FAB authors. So there is no question about the diagnosis of the three cases of APL that are described in this paper. He was an authority; he would not make a mistake.

And the bottom line in this paper was for the first time they demonstrated by fairly sophisticated methodologies, which have now been supplanted by others, that the 15;17 translocation and its molecular byproduct, the PML RAR-alpha gene fusion, could only be identified in a cell that was later than a stem cell, and by their definition a stem with CD34, CD38, negative.

So that basically what they're saying is that based on their study they thought that the cell that was capable of immortality was a cell that was a step beyond the common stem cell that exists in all of us that allows us to repopulate our bone marrow on a regular basis as long as we live.

THE COURT: Let me just ask before you go any further: You said that their finding was that the t(15;17) PML RAR-alpha could only be identified in a cell that was later than --

THE WITNESS: A little later than the blast.

THE COURT: Is this an observational finding?

THE WITNESS: This was done by flow cytometry, by morphology, by cytogenics and molecular genetics.

THE COURT: So when you say "could only be identified," meaning could only be observed?

THE WITNESS: Observed. Correct. Thank you, your Honor.

Now, I like this paper because the implication is that, you know, if the defect by a carcinogen is so early that

it involves the primordial stem cell, one that is resting and only reproduces enough cells to populate us to keep us healthy and then goes to sleep until it has to respond again, and this is going on on a continual basis, why is it -- a rhetorical question -- why is it that we cure anybody? In other words, you have to have somewhere in your bone marrow a population of stem cells that survive the assault of our drug therapy and that are normal. They must be sitting there in a niche somewhere. Otherwise, we would give combination chemotherapy to these patients, we would wipe our their bone marrows, they would become an empty bone marrow like aplastic anemia, which is a very uncommon disease that we see, and there would be no repopulation. So that just, as an aside, makes me think that this --

So this paper was published and it just sort of sat there for about ten years. No other papers that I could find attempted to reproduce this until we come to a very recent paper that is so recent that it's still in press but is available through the wonderful system of the web, and the fact that now we're required to put all our papers up as soon as they've been accepted and not necessarily in hard copy in a journal. So this paper, which is in Leukemia won't be in hard copy in Leukemia for several months, but it is nevertheless available.

Now, this is totally different. What these

investigators did, basically, was to use a mouse model that is susceptible to leukemia, and then they gave us a product that would cause acute promyelocytic leukemia, which is the PML RAR-alpha fusion. So this is not the first time this has been done. In chronic myeloid leukemia, which we call CML, the DCR-able product, which is a result of a fusion of two chromosomes, is able to induce in experimental rabbits a disease that is exactly analogous to chronic myeloid leukemia.

So we know that this -- these products that we can identify in at least 15 to 20 percent of leukemias that we see play a major role in the development of that leukemia. Now, that doesn't tell us what the causative agent was that forced this chromosome abnormality to occur; it just says that once it occurs, this is the triggering product that arrests the cells, does not allow them to grow, crowds out the bone marrow and produces acute leukemia.

Okay. So now let's go to the next illustration. And this is going to blow you away. I'm sorry. And I'll apologize at the outset. The first thing you should see is there are a lot of colors. If you're color-blind, you cannot be a hematopathologist. Impossible. We are totally dependent upon recognition of colors. This is a six-color flow cytometric analysis; in other words, there are six different chromogens, or chromophobes, that have been attached to a variety of proteins, and then the cells are extracted from the mouse and

flowed automatically, and we get the ability to produce these graphs.

And all I want you to appreciate is on the left-hand side there are three boxes. Contained within these boxes are a series of patterns or colors. Each little dot represents a cell. So if you look at the upper left, the big blot of red are promyelocytes and some later myeloblasts. The plot above it are even earlier cells, but they still are in the myeloid family. To the right, the blue color, are normal progenitor cells, the earlier cell to date that any investigator has been able to identify using different antigens and proteins than the paper from ten years ago. Okay. That's the control, all right? No leukemia.

The next panel down is the same animal strains in which the investigators had injected a vehicle. But it's a dummy vehicle; it doesn't contain the gene product that we've been talking about, the ATRA PML. And that's exactly the same. So the vehicle is not capable of causing leukemia. There is no difference. And on the right where it says "progenitors," those are all the developing cells: the megakaryocytes, the erythrocytes, the monocytes. And you can see there's no difference.

The third panel down is the leukemic mouse. So what's happened? The green has disappeared; the blue are only a few little dots left. So what's happened is you get a crowding

effect of the normal stem cells, which are in the upper right, and it's replaced by a huge number of these malignant abnormal promyelocytes that contain the PML RAR-alpha and the 15;17 translocation. And then if you look at the right, everything's gone. Everything has disappeared except the granulocyte macrophage colony, GMC, which you would expect, because those are the progeny of the promyelocytes. And in every case of promyelocytic leukemia, we do see a small percentage of some more mature cells.

The right is just a bar graph giving you a quantitative picture of the qualitative pictures that I showed before.

BY MR. WEATHERS:

Q. Doctor, in the interest of time, let me ask you this question: Do these two papers, together with your considerable experience in this field, inform your opinion as to where the mutation that leads to APL occurs in terms of cell maturation?

A. Both papers strongly suggest -- we can go back to the previous one. No, one more back.

Q. Okay.

A. -- strongly suggests that the leukemic cell is a step beyond the common stem cell. And I've illustrated in the first bullet point that in addition to this study, there are other studies that have shown similar findings with other, rarer types of acute leukemia, one of which is acute myelocytic

leukemia, or in the FAB classification, what we call M5.

Then we can go forward.

So where does this put us? Anybody can do a schemer. And you can do a vertical; you can do a horizontal. It's all in the way you want to try to illustrate what you think is going on in the bone marrow. But I don't know what's going on in my own bone marrow. These cells are all mixed together. They don't have instructions like this, but they do respond to signals that tell them what to do, where to go, when to divide, and when to mature.

So all of these hematopoetic hierarchies, or schemers, basically, are drawn up by individuals who are knowledgeable in the field, may have done research in the field, and are trying to set up a pathway for people to look at and say, you know, it begins with a very long-term cell that is immortalized.

Now, I hope you all appreciate the fact that "immortalized" means you never die. We're mortals. I don't have to say anything further, right? Okay. So we're going to die. That's built into our system. But as long as you live there are stem cells in the bone marrow, in the gastrointestinal tract, in the testicle, that will continue to be produced in the skin as long as you live. So that does not dictate why you die. You die because, unfortunately, we don't have those same kind of stem cells in the heart or the liver or the brain or the central nervous system or the kidneys. So

sooner or later these organs fail or we get cancer and we die. So be it.

Q. Doctor --

A. So if you go down this pathway, based on those two papers I would place the leukemic cell of APL at at least the CMP line, or the GMP line. And it's really just a guess on my part based on those two -- thank you -- observations. But it's a long way from the HSC.

Q. And, Dr. Bennett, just to put this in the context of a slide that we moved past in the interest of time, Dr. Smith's opinion, as stated in his original declaration and elsewhere, is that the mutation occurs which leads to APL and all other AMLs at what he called the pluripotential stem cell, correct?

A. That's correct.

Q. Is that the HSC?

A. Yes. Well, yes, or it might be one step --

Q. We're giving --

A. It's not rocket science, unfortunately.

Now, I would agree with Professor Smith that there are clusters of different types of leukemia that appear to involve more than just a single line. So, for example, in myelodysplasia and some of the secondary leukemias which were mentioned by Dr. Smith where there are chromosome aberrations including, like, Chromosome 5, Chromosome 7, we tend to see a picture in which all of the bone marrow cells, except the

lymphocytes which, your Honor, over on that the right side of that tree share morphologic abnormalities which strongly suggests that you have to go at least above where you have drawn your circle. How far above, no one knows. But as I've indicated, there are several types of acute leukemia that involve just the monocyte pathway or the granulocytic pathway which appear to be what we call downstream rather than upstream of the multipotential progenitor.

Q. And this is, in your opinion, Doctor, unique for APL; that is, the --

A. What I have been describing is unique for APL.

Q. Thank you, sir.

Now, I'm going to pass by this slide. I think we --

A. This just shows us, your Honor, that you can do it vertically or you can do it horizontally. It doesn't make any difference at all. It depends on how you like to look at things.

Q. And just for clarification, the same area would be --

A. That's good right there.

Q. That's where -- on this slide that Dr. Smith used on Tuesday, that's where you believe --

A. Yes. And the authors of the Wojiski paper state that it could be there or it could be one step earlier.

Q. Okay. Thank you.

Conclusion on the cell of origin, Doctor.

A. We've already discussed this so --
Q. All right. Then in the interest of time and being fair to counsel to allow them cross-examination, we'll move on.
Doctor, my question is -- with regards to this next slide, my question is this: First of all, I think at one point Dr. Smith said so far as he knows researchers aren't even looking at the uniqueness of APL as regards benzene exposure and any secondary causes of APL. The paper that we now have up, is that of Dr. Douer?
A. The reason for showing this, I'm a clinical hematologist. I've done some bench research years ago. I'm not a molecular biologist; I'm not a stem cell researcher. Basically, I take care of patients and I make diagnoses, and I've published a fair amount in this area.
Dr. Douer, who is at the University of Southern California and a renowned clinical hematologist, one of the experts in APL, has written a chapter. And that is his statement that I don't need to read to you. So basically, he and I are in agreement. Do we talk at meetings? Yes. Do we write papers together? We are co-authors on some publications. But he is speaking independently from his own personal perspective on APL.
Q. And I've moved to the next slide, and I'll just read the pulled quote from it. "APL is an example of a truly unique and distinct entity within AML because of its distinct clinical,

therapeutic, biological and molecular differences."

Do you agree with that?

A. I agree with that statement.

Q. And Dr. Douer also reached some conclusions as regards whether there are any known causes, either environmental or occupational risk factors, for APL, correct? And in the pulled quote that we have there he concludes by saying, "So far no environmental and/or occupational risk factors have been found for APL."

A. That's correct. I mean, one could modify that a bit by saying that we know that we can cause APL in patients in 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 from Dr. Smith two days ago -- with topoisomerase II that are capable of causing APL.

Now, you have to survive to get it, so, you know, don't be too critical of us, because our attempts are to cure or prolong life of these patients with diseases that would destroy them if we didn't offer them some treatment. But overall, approximately 5 percent of patients that we cure will come down with a secondary AML. And I give lectures on this to staff physicians and doctors at various conferences. And we have a couple of slides that we could illustrate this for you as to how we think about occupational- or therapy-related, or what I

prefer to call event-related, a more generic term. So there are a lot of events that can cause leukemia to occur, and a lot of these have been identified.

Q. I'm going to move on, Doctor --

A. Oh, my.

Q. -- in the interest of time.

A. We're seeing this again, right?

Q. We are. And this needs little introduction. We've talked at length about the Travis study. I simply want to essentially re-create for you a slide that Dr. Garabrant has also already discussed. And I'll represent to you that these are the four alleged APLs from the Travis study, and this is a summary of all of the histological/morphological data contained in the paper.

And I want to first -- with that representation I'm going to first refer you to Case 5 and ask you, sir, to take a look at the data reported and tell me as a hematopathologist, and one with your experience and background, is there enough data about Case 5 to allow you to reach a diagnosis that the individual had APL?

A. Obviously I would have loved to have had the opportunity to review this material myself, but Dr. Lee was chosen by the Mayo Clinic I think partly because -- Number 1, he's an expert; Number 2, he speaks the language, and that obviously helps considerably. My problem with the Travis paper is a little

deeper than that; that is, that Dr. Travis states in various parts of the paper that they were unable to review all of the pertinent material. They had to accept what was told to them by doctors who took care of these patients that they did have what they were supposed to have.

And you have to remember that China went through a horrendous period of ten to 15 years in which their top physicians, their top professors, were out farming and raising rice in the rice patties rather than working at the medical school. So there was a period of time in China, and it still exists today, where the reliability of their database has to be questioned.

What they tried to do, and I give them tremendous credit for this, is to assemble all of this data. And you cannot determine from reading this paper how many slides, microscope slides, they actually looked at themselves. But they did the best they could, they analyzed it as well as they could, and this is what they came up with.

I am perfectly willing to accept Cases 6, 7, 8 as highly likely to be hypogranular promyelocytic leukemia. I make that diagnosis without waiting for the cytogenics to come back, without waiting for the flow cytometry. I feel comfortable -- and I'm sure if Dr. Lee saw those cases -- that's what they were.

Case 5 is the questionable case because, as you remember,

that's the one that we had problems with. When you don't see the granules, is it APL or is it another type of FAB like a monocytic leukemia that can resemble APL? And I can assure you that many of the cases that we see are misclassified because of that observation. Moreover, at the final column, the white count of 1.6 is distinctly uncommon in the variant form of APL. The usual white count is 25- to 30,000 for that particular type of leukemia. And moreover, this is much less common in adults than it is in children. So when you look at that and you say, "Well, how confident are you that Case 5 -- are you as confident as Case 6, 7 and 8," I just don't have that same confidence.

Q. All right, Doctor. You mentioned a moment ago that there are some slides that you use in teaching having to do with therapy-related AMLs and MDSs?

A. Correct.

Q. Is the slide in front of us now one of those?

A. This is one. We can either use this one or use -- there was another -- okay. Let's start with this because I think it's --

Q. And, again, in the interest of time, summarize for us --

A. I'll summarize.

Q. I want to be fair to counsel and give them time to cross-examine.

A. I certainly want counsel to question me, no question.

Okay. So basically what I've done here is to summarize a huge amount of literature which looks at event-related MDS -- or myelodysplastic syndrome -- which is sort of a preleukemia. A big percent of patients with MDS will develop acute leukemia. But they all have a malignant leukemic blast in their bone marrow; it's just a question of how many you count. We have a convention that says until you get to 20, you don't call it preleukemia. 20 percent.

So on my left is the typical alkylating/radiation, so ionizing radiation. Chemotherapy drugs that we used to use for the treatment of Hodgkin's disease, for ovarian cancer, we continue to use for the treatment of patients with lymphomas of all types, like Cytoxan. Everyone agrees that if you've been exposed to these agents, with enough exposure there is a long latency period -- "latency" means from the time of first exposure to the end when the disease is diagnosed. And that exposure is usually somewhere between three and 12 years -- in virtually every paper, and we've written several papers on that.

The verbiage to the right of the arrow says that when you have this kind of leukemia, the vast majority of patients have certain chromosome changes that are seen characteristically. And that was found in going back to the Golomb paper that you heard about yesterday and the day before, Dr. Reilly's work, Mitelman's work. There are innumerable papers that show that.

So there is a characteristic chromosome pattern when you see these secondary leukemias. A primary leukemia in which we cannot identify any cognitive agent -- we call that idiopathic, and you've heard that term used -- you would expect to see abnormalities of Chromosome 5 and 7 no more often that 15 to 20 percent.

So this defines, then, the kinds of changes we see. And it produces a kind of leukemia that is very difficult to treat, unfortunately. So it's bad news twice. You've cured the patient, they come down with this kind of leukemia, and there's not much we can do for them. If they're young, we can offer them sometimes a bone marrow transplant. But basically this is bad news. This is terrible.

Q. Doctor, before you --

A. This accounts for about 85 percent of the events that we see.

Q. And the exposures that you're dealing with here are alkylating agents and radiation?

A. They're well-defined exposures.

Now, it has been thought for a long time, including Dr. Smith until his more-recent studies, that benzene sort of fell into the upper area. If you look at the time, the latency periods where it's been examined, if you look at a few studies that have shown chromosome changes in occupationally exposed individuals, you see a trend that suggests that benzene belongs

up there, at least traditionally.

The second group is the short-term latency. So I had a patient who happened to be married to the head of our veterinarian medicine program -- it always happens that way -- with acute myelocytic leukemia that came on four months after she completed her therapy for Hodgkin's disease. Was in remission with the Hodgkin's disease and had an explosive onset of acute myelocytic leukemia and died within a month. Exposed to a topoisomerase II agent. There are a whole family of these. Some of them appear to be more potent in causing a second event than others. And this was also mentioned by Professor Smith. Mitoxantrone is an anthracenedione not related to anthracycline but functioning in a similar way, and it has the highest incidence of secondary leukemias.

What we find fascinating, and I'll conclude on this, is that if you look at some of the translocations that are described, you'll see some of the same translocations that we see in de novo, or idiopathic, AML. And, indeed, if you are unfortunate to have leukemia but fortunate enough to have this type having been exposed, they're highly treatable. And indeed some of these patients can be cured.

The last point is that none of these patients have a prelude of preleukemia, or myodysplasia. So you can really draw a line between the two columns, and they don't -- they don't cross over. I mean, nothing is pure in medicine. And we

have some patients who have gotten a mixture of both agents, and you'd expect them to see a mixture of chromosome abnormalities and a latency period that is somewhere halfway between short-term and long-term, but that's only in 1 and 2 percent.

The last slide -- the slide before that one, which really just puts this up so that clinicians can understand what we're dealing with. So Class I was the top that I showed you before, the alkylating agents, the radiation. The Class II are the topo II inhibitors. The age tends to be older with the alkylating agents, younger with the topo II.

"Unbalanced translocations"? What that means is that you don't see a reciprocal translocation where the chromosomes maintain all of their material; the chromosome can be lost, or portions can be lost. There is a myelodysplastic phase; there's a preleukemic phase on the first column. The latency period is long, whereas it's short on the other one.

And I've tried to summarize as best I can my own experience, my own publications, on what we have seen on the morphology. And we have published extensively on alkylating agents in ovarian cancer and in bowel cancer. And we have found that a lot of these patients tend to have a type of leukemia that is more recognizable in that category. M6 is erythroleukemia, a combination of bad blood cell precursors and myeloblasts.

And then on the right-hand side we see the other FAB types. And believe it or not, one can even see therapy-related acute lymphocytic leukemia as well as myeloleukemia. And, finally, "Poor response to treatment," clinical response, very likely, with the shorter exposure.

Q. Dr. Bennett, I have one last question for you. Having seen Dr. Smith's original declaration, his supplemental report and now his testimony unrobed here in these proceedings, has anything changed your opinion that you have provided this Court about APL and benzene?

A. No.

Q. Thank you, sir. That's all I have.

CROSS-EXAMINATION

BY MR. STEWART:

Q. Doctor, we've never met before, right?

A. Correct.

Q. Nice to meet you. I'm Al Stewart.

A. Same here.

Q. You saw me earlier go through this exercise with Dr. Bennett, and I would like to do it with you since you sort of understand where I'm heading. What I would like to do is go through basically how much money you have made over the course of 2008, '7, '6 and '5, doing this kind of thing, which I will define "this kind of thing" as providing expert testimony or assistance to defendants in litigation. Can we do that

quickly?

A. Well, number one, I'm not prepared to respond because I did not understand, nor was I told, that I should bring my tax return forms to the courtroom. So what I'm giving you is off the top of my head. And basically, what I can say is my university salary -- number one, I'm 50 percent full time with the university. So that means 20 hours a week. Doctors work 80 hours a week, so you can -- so it's 40 hours. But it's 20 hours a week according to the law. And I get $110,000 for that, okay?

I receive from BioReference Laboratories and Leukemia Research about $50,000, serving as chair of those two organizations. And I give lectures, do -- write chapters for books, royalties from that, and that totals somewhere in the neighborhood of $50,000 a year from the various talks that I give.

I also have a -- provide a service to about eight pharmaceutical companies who are doing studies of leukemia and related disorders, and I sign a contract with them to review those slides for quality control, and they pay me to do that. I give 25 percent of that to the University of Rochester. And that amounts to another 50- or $60,000 a year. I have a microscope at home as well as at the office. So it's a lot of work.

Approximately $70,000 a year to $80,000 a year over the

past four, five years comes from toxic-tort type of work where I give declarations, review pathology slides, confirm a diagnosis, I do a deposition, and rarely appear in court. This is my first time at federal court. And I think I've been in three other court appearances and two workmen's compensation. That's it.

Q. Okay. So let's get back to my question. So that's what I want to get to. My question was: How much money in 2008, approximately, did you make doing this kind of work for defendants in toxic court work?

A. $70,000.

Q. And is that answer going to be the same for '08, '07, '06 and '05, approximately?

A. Plus or minus 10 percent, one way or the other.

Q. Fair enough. So do you want me to do 70- to 80- or make it 70- to 75-?

A. Whatever you want.

Q. I don't care. I want the best approximation that you have.

A. And the reason that it's fixed is because I limit myself. Because of my responsibilities as a journal editor, et cetera, there's just so much time that I can devote to this activity. So it's not surprising that the amount would be the same.

Q. No problem. I'm just looking for that range. 70- to what? What do you want the top number to be?

A. 75-, 80-? Whatever. That's fine.
Q. Great. All right. Now I'm going to go to the next topic. The next topic, Dr. Bennett, is these two papers that you mentioned. You mentioned two papers of Turhan which you mentioned in Blood, true?
A. True.
Q. And then the other paper you mentioned was Wojiski, which isn't technically out, but because of the Internet it's accessible, right?
A. Correct.
Q. So it could change between now and the time it goes to press?
A. No.
Q. It can't?
A. No.
Q. Okay. Fair enough.
Now, with these two articles, the Wojiski and the Turhan, neither of these articles were on your list of reliance materials when you gave a report in this case, true?
A. Correct.
Q. Right. And so on November the 20th, 2008, when you were asked to write a report for us and this Court about what the basis for your opinions were, and you listed on your reference list all the articles for your opinions, neither of those will be found, correct? You listed 14 things --

A. That's correct.
Q. Neither of those.
Okay. Now, what I think you ended up telling this Court was that it is upon the basis of these two articles that you have reached your opinion about what is going on in the stem cell that you've testified about today, true?
A. True.
Q. Okay. So what you've just said is, number one, one of those articles you couldn't have had in your possession because it just came out, so it wasn't the basis of your opinion, correct?
A. Which opinion?
Q. The opinion about stem cells and where -- and where the effect of stem cells happens. At the time of your report.
A. At the time of my report -- yes, that's correct. I mean, this -- these papers support -- give further weight -- to my opinion that I offered previously.
Q. I understand that. But I guess my point is when you rendered your opinion in your report, you didn't have any papers that you cited for that support, correct?
A. That's correct.
Q. And yet it was your opinion, even without the papers, right?
A. Yes.
Q. You didn't feel like you needed these papers to have that

opinion, right?
A. At the time I wrote the letter, that's correct.
Q. Right. And then when you wrote -- after you wrote the report you gave a deposition, correct?
A. Correct.
Q. And at the time of that deposition, you didn't have either of these papers, correct?
A. Correct.
Q. Uh-huh. And even though you didn't have those papers, you formulated the opinion that you have in this case that you've expressed to this Court, and you were able to formulate that opinion without any scientific paper that you had in your possession supporting that opinion, correct?
A. That's correct.
Q. So, sir, it's safe to say, isn't it, that after your report and after your deposition, that you went out and found two papers to support your opinion, right?
A. Yes. I was concerned about the brevity of some of my remarks at the deposition and some of the problems that we had with communication, and dropping the line and so forth. And when I read over the deposition, I realized that my statement was overly broad and I modified it. And that was appended to the pages that I subsequently submitted to the deposition.
Q. Yes. And so, Dr. Bennett, I guess my point is this, and tell me if you agree with this: that you were able to reach

your opinion on the subject of the initiation of leukemia in stem cells without scientific papers to support it, right?

A. Without these two papers; that's correct.

Q. Yes.

A. And that was based on my judgment, as I previously indicated, a review of the literature that I had available to me at the time, and my sense that this type of leukemia was extremely unique.

Q. Okay. But, Doctor, there are no other papers that you cited in support of this proposition besides these two, correct?

A. Correct.

Q. All right. Now, with respect to this opinion that you have, there's not universal agreement that this is actually the way things happen with leukemia in the stem cells, true?

A. I don't know.

Q. Well, there weren't so many papers out there that you were able to list them in your report, November 20, 2008, true?

A. When you asked whether there was universal agreement, I'm a sole person of a very large universe, and there's no way that I can have discussions with the entire universe, as you define it.

Q. That's fair. I'll change the question.

A. Thank you.

Q. You would agree with me that there are reasonable

scientists in your field that disagree with your opinion on how leukemia occurs via stem cells. You would agree with that, right?

A. I'm sure there are.

Q. And those people are not unreliable people, true?

A. I can't attest to that; I can just agree with your first statement.

Q. Fair enough.

Now, I want to go to -- well, let's just back up. Dr. Smith -- you believe that Dr. Smith disagrees with your view of what's happening with leukemia in the stem cells, correct?

A. Well, my recollection is that Dr. Smith was impressed by this Wojiski paper and felt that more research needed to be done. And, indeed, if you read the paper carefully -- and I've read it probably 50 times because it's not easy -- the authors do not rule out the possibility that the leukemic event couldn't have occurred at an earlier point, but that there's no way that they can detect that.

Q. Understood. And I want to put this up on the chart that we have all seen just so we're comparing things. What I think I hear you saying --

A. My Xs came back.

Q. Yeah, well, this was in your original slide.

What I think that you're saying here is even the Wojiski authors agree that it is consistent with their paper for these

events to be occurring with respect to APL prior to here, correct?

A. Yes. What they say is -- you can move the pen back at least one level and possibly another level.

Q. Correct.

A. Right there.

Q. And, Doctor, isn't it true that at this level with this cell, this cell can become all these cells that it has lines to, correct?

A. Correct.

Q. All right. So by an effect on the stem cell at this level, if that effect occurs, it could become erythrocytes, platelets, neutrophils, monocytes, eosinophils, basophils, true?

A. The reason I said that I can support this cell being a cell of interest, if you want to use the legal sense, because we know that there are cases like chronic myeloid leukemia in which the Philadelphia chromosome, which identifies the defect in CML, can be found in all of those cells that you listed until you get down to the lymphocytes line. So clearly the CFU-GEMM is a target cell for chronic myeloid leukemia. Now, having said that, the only known cause of chronic myeloid leukemia that has been associated with exposure has been ionizing radiation.

If you're going to suppose that that cell can be hit by,

say, benzene, and only produce neutrophils or promyelocytes and their progeny, I know of no biologic mechanism that has ever been considered that would say that there is that type of permissive behavior. It is much more likely that if that cell became malignant because it has built in the potential to do anything, it would do anything. And that is what usually happens with malignancy. With most cancers, the cancer recapitulates as best as it can the normal environment. And the normal environment for the CFU-GEMM is to move to all of these various compartments.

Q. Well, let me just try and say it simply: This Wojiski paper that you have recently seen and you are now relying on, the authors themselves say it's consistent that the stem cell event is happening before X and right here, correct?

A. No. What they say is that they can't rule out the possibility that there is a latent cell that their techniques do not allow them to identify.

Q. Yes. And you basically told us, I think in very simple terms, that rules in this cell here -- or this stage here and this stage here, true?

A. As I indicated previously, this isn't happening. This is only happening in the minds of people who decide they want to show a flow diagram. So we don't know what's going on in the bone marrow. So this is as good as we could get.

Q. All right. Let's move --

MR. STEWART: What's your pleasure, your Honor? It will be a little --

THE COURT: Go ahead. Go ahead.

MR. STEWART: Great.

BY MR. STEWART:

Q. Let's move on to another issue, and that issue is the fact that you don't view yourself as an expert on the relationship between benzene and AML, true?

A. True.

Q. Now --

A. Correct.

Q. In contrast to that, Dr. Bennett, you do view Dr. Smith to be an expert on the relationship between benzene and AML, true?

A. True.

Q. And as a matter of fact, you consider him to be such an expert that you invited him to be one of the principal authors for the chapter in your book entitled "Causative Agents in the Etiology of Myelodysplastic Syndromes and the Acute Myeloid Leukemias," correct?

A. Absolutely correct.

Q. Yes. Now, Doctor, I know this is apparent, but I want it to be in the record. You did not invite Dr. Garabrant to write this portion of your book, did you?

A. No, I did not.

Q. You did not invite Dr. Pyatt to write this portion of the

book?
A. No, I did not.
Q. And you did not invite yourself to write this portion of the book?
A. I would never think of doing that.
Q. All right. Fair enough.
Now, you did edit this book, though, correct?
A. Yes. We have a second edition out that just came out a few months ago, but we have no section on epidemiology since it really hasn't changed very much. So that's why no one else was invited.
Q. Okay. Fair enough.
In this book -- in this chapter, your book says, "Although benzene has been most strongly associated with AML and aplastic anemia, there is evidence to suggest that other subtypes of leukemia, MDS, non-Hodgkin's lymphoma, and possible other hematopoetic and lymphoproliferative malignancies and related disorders are linked with this exposure to this chemical," correct?
A. Yes. And he referenced some nine articles to support that statement.
Q. Yes, he does.
Now, you would agree, wouldn't you, Doctor, that there have been innumerable studies that demonstrate that benzene actually works at multiple levels to create damage to the DNA

structure of the hematopoietic system, true?
A. That's an overly broad statement, but by and large, most studies show that benzene -- it's not obviously benzene because benzene does not cause the damage; the hydroquinone has to be metabolized to that active compound. But let's say that the studies are consistent that show that a variety of different cells in animals and patients, primarily lymphocytes, can be damaged by benzene, which strongly implicates benzene as causing damage to DNA.
Q. Okay. Let's do it this way: You gave testimony in, let's see, the case of Hooper versus Bridgestone Tire, and I believe Chevron was in that case as well, August 8, 2005. Yes?
A. Yes.
Q. And in that case you were asked this question: "And there have been enumerable studies that demonstrate that benzene actually works at multiple levels to create damage to the DNA structure of this hematopoietic stem cell; isn't that correct?"
And you answered "yes," correct?
A. Yes.
Q. And then you were asked, "And so this hematopoietic stem cell is sort of the mother cell. All of these cells that we see on the chart are flowing from the stem cell; isn't that correct?"
And you answered "correct," right?
A. Correct. That's the flowchart we looked at earlier.

Q. Now, you're familiar with the studies done by the National Cancer Institute through Dr. Smith that showed low-dose exposures, doses of less than one part per million, showing chromosomal damage to progenitor stem cells, true?

A. You're talking about in vitro studies now?

Q. I'm talking about the Qu-Smith article; yes.

A. Dr. Smith and his group have written several articles on damage of cells and using different techniques and so forth; yes.

Q. Well, let's look at how you answered this question in 2005. You were asked this question: "Are you familiar with the recent studies done by the National Cancer Institute of low-dose exposures, doses less than one part per million, showing chromosomal damage to these progenitor stem cells?"

You said, "I'm not sure which article you are referring to."

The lawyer said, "The Qu article."

And you said, "Is that Qu, Smith, et al?"

The answer was "yes," and you say "yes."

Here's the question: "And they have written in research, in fact, Dr. Martyn Smith -- in fact, most of that group is associated with the Berkeley -- University of California at Berkeley; isn't that correct?" And you answered "correct."

And the question was, "And they have recently published under a grant, 'Cellular Effects Generated by Benzene'; isn't

that correct?" And you answered, "That is correct."

And then the question was, "And they are of -- they have shown multiple levels of chromosomal damage done at exposures below one part per million; isn't that correct?" And you answered, "I believe that is true," right?

A. You're reading it.

Q. Well, that's what you testified to.

A. I can't argue. Right.

Q. Okay.

A. Okay.

Q. Now, you know that Dr. Pyatt has been deposed in this case, right?

A. Yes.

Q. You read his testimony?

A. Deposition?

Q. Yes.

A. Yes.

Q. Okay. So with respect to Dr. Pyatt, I want to know if you agree with Dr. Pyatt's statement -- and I will show it to you -- his statement that says, "The progenitor cell, hematopoetic progenitor cell population is a target issue for benzene toxicity." Do you agree with that statement?

A. No. I think it's a matter of -- when I showed the illustration of being absolutely crystal clear to be very, very specific about what is the progenitor cell, what is the

hematopoetic stem cell, what is the cell that leads down the myeloid pathway. And I think there can be, often, confusion in terminology.

Q. All right. Well, let's try this -- let me ask you one other question about this deposition and then I'll ask you something further.

Dr. Pyatt also told us in his deposition -- and I will read this to you. It says, "With respect to the last question that I just asked you about the different subvariants of AML and the extent to which they arise from the same progenitor cell, is that issue something that you would say reasonable scientists could disagree about?" And Dr. Pyatt says, "Reasonable scientists do disagree."

Do you agree with that statement by Dr. Pyatt?

A. I'm sorry. You'll have to put that back up again because you're reading from what Mr. Leghorn said. It says, "Mr. Leghorn: Object to form. Reasonable scientists do disagree."

Q. That's not Mr. Leghorn --

A. "A" is from --

Q. That's Dr. Pyatt.

A. Okay. "Reasonable scientists do disagree." Okay.

Q. All right? And what I'm asking you: Do you agree with Dr. Pyatt that reasonable scientists can disagree about the difference subvariants of AML and the extent to which they arise from the same progenitor cell?

A. Yes.
Q. All right. So on this issue of your opinions on subvariants of AML and where they arise, you've looked at the literature and come to a conclusion -- made scientific judgments about that and come to a conclusion, correct?
A. Correct.
Q. Dr. Smith has done the same thing, read literature and come to conclusions, correct?
A. Correct.
Q. All right. He has not come to unreasonable conclusions, has he?
A. From my perspective, he has come to an unreasonable conclusion, yes.
Q. I understand you disagree with his conclusion --
A. I disagree with his conclusion.
Q. -- but you would agree that reasonable scientists can and do disagree with you, true?
A. Correct. I would hope so.
Q. Now, I want to talk about the Douer paper that you talked about.
A. It's not a paper; it's a chapter. It's just a review.
Q. It's just a review?
A. It's a review of a chapter in a textbook, review of AML.
Q. All right. Now, you pointed out that this says, "It is unknown whether the risk for APL is associated with any

environmental or occupational exposures," right?
A. That's what he said.
Q. Yes. But isn't it true that when you looked -- went and looked at the literature, you said there have been occupational exposures that have been identified, right?
A. Oh, you're referring now to the Italian cohort cases that I -- yes.
Q. Right now I'm referring to what your report --
A. Okay. Fine. Right.
Q. And you say in your report, "Two Italian cohort case-control studies have identified certain occupational exposures as potentially having a higher risk. These including shoemaking" -- and you have an odds ratio there of 6.3, correct?
A. Correct.
Q. You would consider that a significant association, wouldn't you?
A. Yes.
Q. And, in fact, you know that in that paper it's a statistically significant association, true?
A. Yes.
Q. And this is the Mele paper that we were talking about earlier?
A. Right.
Q. And you understand that these authors in this Mele paper

believe that this relationship could be related to benzene, true?

A. They suggested that.

Q. Yes. That's not an unreasonable suggestion, is it, Doctor?

A. Based on their study it's not an unreasonable suggestion.

Q. Yes. So when you mentioned the Douer paper, he doesn't mention -- Douer doesn't mention in his discussion any of the things that you found, does he? He doesn't talk about shoemaking or electricians or agricultural and textile workers or machine operators, does he?

A. I think, with due respect to Dr. Douer's report, what he was assuming was sort of a global analysis or inference about the scope of the literature, and comes down on the side of there's not much out there. You can always find one or two articles to support a claim of relationship. And, again, it's based on the weight of the evidence and the number of articles that have appeared.

Q. Yes. But to suggest --

A. I can find nothing wrong with either of the two Mele papers as far as what they did, nor -- I know several of their workers -- met them at meetings -- and their capacity to make proper diagnoses.

Q. Yes. But to suggest that what Dr. Douer is saying lays out for readers what the studies are, what they say to evaluate

them, he didn't do that in his study, did he? And it's not a study, it's a review paper. I apologize.

A. It's a review paper, and he's limited by amount of time and effort he could put into it.

Q. So simply what we have here is Dr. Douer's opinion in a review paper?

A. Yes.

Q. Okay. Let me ask you this question: You testified that APL may arise at the CMP progenitor level, right?

A. Yes, I believe so.

Q. Yes. Isn't it true that all of the various types of AML involve abnormalities in cell types that all descend from the CMP progenitor cell?

A. No, I think I indicated that it's a granulocyte, not the -- the CMP is earlier -- a little earlier stage. And the authors indicated that it was the granulocyte precursor cell. The CMP is a more multifocal type of cell. But what they're inferring is that they can't rule that out; that's correct.

Q. I didn't actually ask about that study. I asked isn't it true that all the various subtypes of AML involve abnormalities in cell types that all descend from the CMP progenitor cell?

A. All the myeloid cells descend from that common precursor cell.

Q. Yes.

MR. STEWART: I'm done with my cross-examination.

THE COURT: Okay. Let me just ask, Doctor: I think you referred to something as "the malignancy event." Is that -- or a -- that is, when the healthy cell becomes malignant or leukemic. Is that -- am I touching on a concept that I'm accurately recalling or not?

THE WITNESS: Well, when a healthy cell is -- take any healthy cell in the body. When it becomes malignant, it then has the capacity to continue to reproduce itself without maturing. Without maturing. Now, it can mature a little bit. So, for example, in colon cancer, we can see well-differentiated colon cancer or we can see poorly differentiated colon cancer. And that's all based on signal coaching that exists within the tumor.

THE COURT: I may have gone down the wrong line. What I'm interested in is the so-called leukemic stem cell. Maybe I can just ask you to tell me what that is.

THE WITNESS: The leukemic stem cell is a cell that has been identified that is capable of continually reproducing itself and not maturing, not developing into normal developing cells like neutrophils, pus cells, monocytes and so forth.

THE COURT: But it's a stem cell in the sense that it both reproduces itself and generates other cells?

THE WITNESS: No, not the latter; the former.

THE COURT: Isn't that what a stem cell does?

THE WITNESS: Well, that's why these terms are so bad,

and you're correct in having concern about the terminology. So the normal stem cell -- the normal stem cell -- receives responses where it sits in the niche in the bone marrow, that triggers it to release a flood of cells that are capable of maturing and repopulating, keeping the peripheral blood system intact.

As soon as it does that, one of two daughter cells stops producing and goes to sleep until it gets another message. Then it wakes up, reproduces itself, goes back to sleep. The leukemic cell never sleeps. It's incapable of sleeping. So it just continues to reproduce itself; it divides, it divides, it divides.

Now, the rate of division is very much dependent upon the kind of leukemia or lymphoma that we see. So there are some tumors that divide very rapidly, like small-cell lung cancer, or Burkitt's lymphoma in which the cell literally divides and doubles itself every 24 hours. Horrendous growth rate. There are some, like in MDS, in which the growth rate is so slow that the patient may live for ten years before that leukemic cell divides enough to become acute leukemia and crowd out the bone marrow. So it's highly variable.

But by definition the leukemic -- once we say "leukemic stem cell," we are saying a cell that is immortal unless we impact on it with treatment.

THE COURT: So that characterization doesn't

necessarily say anything about the stage of maturation at which that occurs?

THE WITNESS: No.

THE COURT: Okay.

MR. STEWART: Can I just follow up?

THE COURT: I was going to give him a chance and then you.

REDIRECT EXAMINATION

BY MR. WEATHERS:

Q. Two quick things in the interest of not pressing the Court's patience any more than we have.

A. The Court has been very patient with me, I must say.

Q. Doctor, the Wojiski paper: Counsel took you through the fact that the authors of that paper can't rule out that the mutation leading to APL could have occurred at an earlier stage, correct?

A. Correct.

Q. But they've reached a scientific conclusion from their work, didn't they?

A. They did. That it was unlikely based on their work, right.

Q. But they reached a conclusion as to where they thought it occurred?

A. Right.

Q. And what was that?

A. At a later stage.
Q. All right. And one last thing. There was talk about the book in which Dr. Smith kindly wrote a chapter for you. When was that book published?
A. Ten years ago.
MR. WEATHERS: Thank you. That's all I have.
THE COURT: Mr. Stewart?

RECROSS-EXAMINATION

BY MR. STEWART:
Q. Yes. The version of the book I have --
A. '92? '94?
Q. The version of this book that I have was copyrighted in 2002.
A. So it -- 2002 means that it was put to bed around 1998 or '99, because it takes that long to get the chapters in.
Q. Fair enough. Here are my -- I'll move to the microphone.
Here are my two questions: Isn't it true a leukemic stem cell can result in different variants of leukemia?
A. Yes.
Q. And most scientists think this is a multistep process, so that more than one event or attack on the cell line must occur before you see full-blown leukemia?
A. So the latter is more in question, in my mind, than the former.
MR. STEWART: Fair enough. That's all I have.

THE COURT: All right. Thank you very much, Doctor.

We'll recess until tomorrow morning.

MR. WEATHERS: Thank you.

THE CLERK: All rise.

Court is in recess.

(The proceedings adjourned at 1:25 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