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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA
Civil Action No. 93-0561 (HHG, DAR)
BETSY LAKIE,
Plaintiff,
vs.
SMITHKLINE BEECHAM, et al.,
Defendants.

DEPOSITION OF RICHARD D. IRONS
April 12, 1996
1860 Blake Street
Fifth Floor
Denver, Colorado

A P P E A R A N C E S

HARVEY S. WILLIAMS, Esq. 1019 19th Street, N.W.
Suite 800 Washington, D.C. 20036
Appearing for the Plaintiff.
DANIEL W. WHITNEY, Esq.
HOWELL, GATELY, WHITNEY & CARTER Twelfth Floor
401 Washington Avenue Towson, Maryland 21204
Appearing for the Defendant
SmithKline Beecham.

The deposition of RICHARD D. IRONS, produced, sworn and examined upon oath on the 12th day of April, 1996 at 10:04 a.m., at 1860 Blake Street, City and County of Denver, State of Colorado, before me, Jessica Swaim, a Registered Professional Reporter and a Notary Public within and for the City and County of Denver, State of Colorado, pursuant to the Federal Rules of Civil Procedure for the examination of the said RICHARD D. IRONS, a witness called for examination by the plaintiff herein.

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RICHARD D. IRONS,
being first duly sworn to state the truth, the whole truth and nothing but the truth, testified on oath as follows:
EXAMINATION
BY MR. WILLIAMS:
Q. State your name for the record, please.
A. Richard D. Irons.
Q. And what is your occupation, sir?
A. I'm a toxicologist at the University of Colorado Health Sciences Center.
Q. How long have you had that position?
A. Since January 1989.
Q. I'm going to show you what we'll mark as Exhibit 1, and ask if you can identify that.
A. It's a deposition notice.
Q. Is that for the deposition today?
A. Yes.
Q. Did you receive a copy of that prior to today?
A. I saw it briefly yesterday.
Q. Okay. Were you able to bring the documents requested?
A. Some o= them.

Q. What weren't you able to bring?
MR. WHITNEY: We object to category 7 and 18 as usual.
MR. WILLIAMS: Did you fax 12 to my off ice?
MR. WHITNEY: Yeah. And also we object to item 14, which is sort of a conditional objection, since I'm not quite sure of the status, if one of the documents is responsive. That relates to a report in another opinion case. And I don't want to breach someone else's work product. So I need to contact those attorneys to find out exactly where the case is.
MR. WILLIAMS: Is that a case that Dr. Irons is working on?
MR. WHITNEY: (Indicating.)
A. Eleven, to the extent that I have submitted the report, my report in this case.
Q. (BY MR. WILLIAMS) okay. Paragraph 11 refers to cases where you've testified either in deposition or at trial; correct?
A. Yes.
Q. The list of cases I have were started in 1992 through 1995. Is that what you're referring to?

A. Yes.
Q. Did you have any-- did you participate in any litigation prior to 1992?
A. Yes. I don't have any record of those cases. That is what I had at the time that I responded to the report, the report submission.
Q. Okay. Did you bring a copy of your report that you submitted in this case?
A. Yes.
Q. Are the cases listed on your CV or on your report?
A. Neither. It was submitted with the report, but it's not attached to the report. This is just a copy of the report.
Q. Okay. And did you bring the list of the cases with you here today? Is it with you?
A. No.
(Whereupon, documents were marked Irons Deposition Exhibits 1 and 2 for identification by the reporter.)
A. Twenty-one in particular and to a certain extent 22, I did not attempt to bring every article or manuscript that I possess relating to benzene or myelodysplastic syndrome. It would be in the thousands.

Q. Okay. Did you bring all the articles which are relevant to your opinions in this case?
A. I believe so, yes.
Q. Okay. I want to refer again to Exhibit 2. Can you identify this for the record?
A. Yes.
Q. And what is Exhibit 2?
A. It's a list of cases that I've testified in either by deposition or trial testimony from 1992 through the time that I submitted my report, which was in September 1995.
Q. Okay. Is this a complete list of cases from 1992 to the-
A. It's-- they're-- I have given, I believe, two depositions since then. It is complete, as I recall, up until September 1995.
Q. And that was the last case listed as Lavender V. Miles?
A. Yes.
Q. What cases were you involved in subsequent to Lavender?
A. I have given a deposition in a case called Poston V. Monsanto.
Q. Is it P-o-s-t-e-n?
A. It o-n, I believe.

Q. When was that deposition?
A. It may be-- that was given I believe-
it was either late 1:95 or early January. I think it
was late 1995.
Q. And what's the jurisdiction of that
case?
A. Texas.
Q. Is it in U.S. District Court?
A. I believe it was state court,
Galveston.
Q. And do you know who the attorneys are
in the case?
A. The case is settled. It's no longer
pending. The attorneys were Jeffrey Kilgore-
Q. He was the attorney for the plaintiff?
A. Plaintiff. And-- let's see-- I believe
it was Robert Jones.
Q. Was the attorney for Monsanto?
A. Yes.
Q. Were you working for Monsanto in that
case?
A. Yes.
Q. Do you have information on you today as
to the phone numbers or addresses for Jeffrey
Kilgore?

A. No.
Q. Would you have that in your office?
A. No, not to my knowledge.
Q. Would you have the case number-
A. No.
Q. -- of the case?
A. No.
Q. You know when it settled?
A. I believe it was December 1995. I'm not positive though.
Q. Okay. Did that case involve exposure to benzene?
A. Yes. That was the allegation.
Q. What type of exposure was it?
A. Occupational.
Q. Do you know what the levels alleged were?
A. No. I don't recall.
Q. Did you prepare a report in that case, as you have in this case?
A. I believe so.
Q. Do you recall what the disease manifested by the plaintiff was in the case?
A. It was multiple myeloma.
Q. Were there any other chemical exposures

other than benzene?
A. I don't recall the specific allegations. I believe benzene was certainly the major chemical that was at issue in the case.
Q. Where was the plant where the exposure occurred?
A. I don't recall. It would be Texas.
Q. Okay. Texas refinery?
A. I'm not sure it was a refinery. It may have been.
Q. Okay. And other than the Poston Versus Monsanto case, have there been any others?
A. Testified in a case called McFarland.
Q. McFarland is the plaintiff?
A. Was the plaintiff. The defendants in that case were a group of insurance companies.
Q. Do you know the name of the group?
A. I think Hartford was one of them.
Q. Did that case involve a chemical exposure?
A. The allegation was benzene again, and the disease was multiple myeloma.
Q. What type of exposure?
A. Again, I don't recall. Basically my testimony in both of these .cases dealt primarily with

causation, and the exposures were not as important to my opinion as the nature of the disease.
Q. Your opinion was that benzene does not cause multiple myeloma?
A. That's correct.
Q. Under any set of circumstances?
A. Under any set of circumstances.
Q. When did you testify in that case?
A. It was over the same period, so it was in the late-- it was the fall or winter of 1995.
Q. And where is that case pending?
A. I believe again that case is settled. It was-- I believe it was set in Calcasieu Parish, Louisiana.
Q. And do you know who the plaintiff's attorney was?
A. Herschel Hobson.
Q. Hobson?
A. Hobson.
Q. Do you know where his office is?
A. I know. I'm blanking. East of Houston.
Q. His office is in Texas?
A. Yes. Lubbock. Lubbock, Texas.
Q. And the defendant's attorneys.

A. Jeffrey Balfour.
Q. Is he in Louisiana or Texas?
A. Take Charles.
Q. Was it federal court or state court?
A. The state court.
Q. Do you know the case number?
A. No.
Q. Was it in Lake Charles court?
A. It never got to court, so I don't recall specifically where it was set. I do believe it was in Calcasieu Parish. I recall that.
Q. Which parish?
A. Calcasieu.
Q. Okay. Do you know where the exposure occurred in that case?
A. I don't recall the specifics at this time.
Q. Other than those two, are there any other additional cases?
A. Those are the only cases that I've testified in since the time of this report.
Q. Do you have the information I've been asking you about those cases with regard to the attorneys' names and where the cases were pending? Do you have that information for the

cases listed on Exhibit 2?
A. In certain-- in some cases, yes; in some cases, no. This was constructed from memory, and I don't have complete information on all of them. I have no case number information. on any of them.
Q. Okay. Would you mind getting what information you have that's responsive to this paragraph 11 of the deposition notice with regard to those other cases?
A. To the extent that I can recall that, I can do that.
Q. Okay. Thanks. I have a question on paragraph 14 of the deposition notice. Have you been consulted or are you working on any case involving myelodysplastic syndrome?
A. Yes, I am.
Q. Where is that case pending?
A. Beaumont, Texas.
Q. Are you working for the plaintiff or the defendant?
A. Defendant.
Q. Who is the defendant?
A. It's a group of defendants. I'm not sure I can name to you who the companies are.

Q. Is it a benzene exposure case?
A. That's the allegation. I've seen no information that would lead me to believe that there was any exposure to benzene.
Q. The allegation, though, is the chemical-
A. Yes.
Q. -- involved in the case is benzene?
A. Yes.
Q. And the disease alleged is which one of the four listed?
A. It's a refractory anemia.
Q. Simple refractory anemia?
A. Yes.
Q. Which would also be myelodysplastic syndrome; right?
A. Refractory anemia is included within the broader rubric of myelodysplastic syndrome.
Q. Okay. Was this an occupational exposure?
A. That's the allegation.
Q. Okay. Do you know who the plaintiff's attorney is?
A. Herschel Hobson.
Q. Have you rendered an opinion in that

case?
A. Yes.
Q. Have you issued a written report?
A. Yes.
Q. And has that been provided to the plaintiff's attorney?
A. To my knowledge. I don't have any direct knowledge of that.
Q. Has suit been filed? I guess it has.
A. Pardon?
Q. Suit has been filed in this case?
A. Yes.
Q. Is it pending in Texas?
A. Yes.
Q. In Beaumont, Texas?
A. Yes.
Q. State or federal court?
A. State, I believe.
Q. And I take it you haven't given any testimony yet in that case?
A. No.
Q. Other than that case and this case, have you been asked to give an opinion as to the cause of myelodysplastic syndrome in any litigation?
A. I don't believe so.

Q. And in the Beaumont, in the case we've just been talking about, you know the plaintiff's name?
A. Castro.
Q. And the defendant is a group of companies?
A. I believe so.
Q. Is it insurance companies or-
A. I believe it's chemical companies.
Q. And in that case I take it your opinion is that there was no exposure?
A. That's an oversimplification of my opinion. My opinion essentially is that the presence of refractory anemia in and of itself does not constitute evidence of exposure to benzene.
Q. What would constitute evidence of exposure to benzene?
A. Well, it would depend on-- in an occupational setting one has industrial hygiene data or information relative to the amount of benzene that is available, the opportunity for exposure, the potential concentration of benzene, the use of benzene, and an itemization of the conditions under which it's used, whether or not the individual used protective equipment. A variety of issues relate to

the potential for exposure.
Q. I take it then that, if there was evidence of an exposure, would refractory anemia be evidence of benzene toxicity?
A. If there was sufficient exposure to benzene in a chronic environment to induce bone marrow injury, one would not expect to see a simple refractory anemia per se, but refractory anemia would be among the constellation of effects that you might expect from chronic exposure to high levels of benzene.
Q. Other than the cases we've been discussing, are there any others that you haven't mentioned that you've been involved with since '92?
A. To the best of my recollection this list is complete, but it may not be. As I said, it was constructed from memory. I believe it's essentially complete.
Q. Okay. In any of the cases in Exhibit 2, did you testify on behalf of the plaintiff?
A. Yes.
Q. Which one?
A. Anschultz Versus National Semiconductor.
Q. What was the issue in that case?

A. It was lead.
Q. Lead poisoning?
A. Lead environmental contamination.
Q. On all the others have you testified on behalf of defendants?
A. That's correct.
Q. Are these defendants all either petroleum companies or chemical manufacturers?
A. KNE Energy is a utility company.
Q. What was the allegation in that case?
A. Environmental contamination.
Q. From what?
A. Benzene.
Q. What was the disease in that case?
A. That's a very good question. It was a community. There were two hundred plaintiffs. To the best of my recollection there were no cancers and leukemias in the group.
Q. Was there any other evidence of bone marrow toxicity in the group?
A. No.
Q. There was no blood dyscrasias?
A. No.
Q. No myelodysplastic syndromes?
A. No.

Q. Other than in KNE Energy, are the rest of the companies either chemical manufacturers or petroleum-related industries?
A. I believe so.
Q. How many of the other cases involve benzene as an element of the cause of action?
A. Seven or eight.
Q. I guess I should ask you to identify the cases rather than just count them. Which ones involve benzene exposure?
A. Albertson.
Q. What type of exposure did Albertson involve?
A. The allegation was ground water contamination.
Q. From what?
A. From a regional distribution site.
Q. Was this a regional petroleum product?
A. No. Natural gas.
Q. Was there just one plaintiff or multiple plaintiffs?
A. It was a group of plaintiffs.
Q. Do you know what the diseases alleged were?
A. No. As I said before, it was a large

list of miscellaneous.
Q. I'm sorry. Is that the same-- is that the-- oh, that's the same case we just discussed. I didn't realize that. I'm sorry.
A. Yes.
Q. What's the next one that involved a benzene exposure?
A. LeBlanc Versus City Services.
Q. Was that an occupational exposure?
A. Yes.
Q. And what type of disease occurred in that case?
A. I believe it was a-- there were a couple of plaintiffs in that case. I believe it was multiple myeloma and a non-Hodgkin's lymphoma.
Q. Okay. What do you have next?
A. Choate Versus Amoco.
Q. What type of exposure did that involve?
A. Occupational exposure.
Q. What was the disease?
A. Multiple myeloma.
Q. Is that case in Texas also?
A. Yes.
Q. You remember who the plaintiff's attorney was?

A. I think it was Jeffrey Kilgore.
Q. And which case is next on the list that was a benzene exposure allegation?
A. Dendinger Versus Kaneb Pipeline.
Q. What type of exposure was that?
A. It was a gasoline storage container underground leak. I believe the allegation was benzene. It was a property case.
Q. Do you remember the disease in that case?
A. I don't believe there were any.
Q. Okay. Were the plaintiffs alleging benzene exposure and a disease?
A. I believe benzene was the principal compound in the complaint, but gasoline was the substance that was at issue.
Q. Benzene is contained in gasoline, right?
A. Pardon?
Q. Benzene is contained in gasoline; is that correct?
A. There are trace amounts of benzene in gasoline.
Q. What is a trace amount?
A. A very small amount.

Q. Is there a number which is in your mind when you say trace amount or a range?
A. In the United States today, on average you're looking at somewhere between a fraction of a percent and maybe as much as two percent.
Q. So up to two percent would be considered trace?
A. With respect to the potential for contamination or exposure to benzene, yes, I would call that trace.
Q. Is that a standard that is set in terms of petroleum products by any organization?
A. Pardon? I don't understand the question.
Q. Is there a level placed on how much benzene can be in gasoline?
A. I think in general the focus is on minimizing the amount of benzene that's present in gasoline. So it's usually much less than two percent. In Europe it tends to be more.
Q. What would it be called if it was five percent in terms of the amount?
A. If it was five percent or greater, five percent is often arbitrarily used as a benchmark with respect to a product having a significant amount of

benzene, certainly as a solvent. Generally levels below five percent do not tend to pose a significant hazard with respect to transient exposure to the product, certainly in the atmosphere, as far as benzene is concerned. Below that the exposure to benzene is minimal.
Q. Below five percent?
A. Usually, yes.
Q. So would anything under five percent be considered trace?
A. The term "trace,, refers to, in strict terminology, the measurement of small amounts of the substance. With respect to the amounts of benzene that are normally found in the air, using gasoline products of two percent or less, the amounts that are present are usually one part per million or less in the air.
Q. In the air, in a workplace; is that what you're referring to?
A. Yes.
Q. You're not referring to the air-
A. Well, with gasoline I'm talking about conditions under which you will normally be pumping it, such as when you fill your tank at a gas station.
Q. Okay. So even in an outdoor space,

you're saying it would be one part per million?
A. Within the breathing range of an individual pumping gas, one part per million is certainly what the EPA calculates as the average potential exposure to benzene in the pumping of gas.
Q. And has that been determined with regard to this trace amount that you've been referring to?
A. I don't understand the question.
Q. If the product has two percent or less of benzene in it, the gasoline, would that-- is it your understanding that that's been calculated to result in an ambient air level of one part per million?
A. It isn't calculated. What I'm saying is, when the EPA has measured the amount of benzene in the air in and around, in the vicinity of individuals pumping gasoline, that that is the level that they see normally associated with that operation. It's not a calculation per se.
Q. Have they published these findings?
A. Oh, yes.
Q. Where are they published?
A. Several places. I believe one of the articles I brought refers to that.

Q. Do you know -he name of the article?
A. It's by a min named Wallace, Lance Wallace.
Q. Was it one of the articles you attached or you referenced in your report?
A. Yes.
Q. You don't need to get it out. Is the term "trace amount," is there an industry or commonly accepted understanding of that term in the industry?
A. "Trace" is a term that is used by analytic chemists or toxicologists usually to refer to detectable but unquantifiable amounts of a substance in another. That's the-- that is in fact the precise definition of "trace".
Q. What does "unquantifiable" mean?
A. It means that the levels are not determinable based upon the sensitivity of the method accurately enough to place a number on them.
Q. I suppose then that one percent, that would be a number-
A. When I first used the term "trace," I was using it loosely. I was not using it to refer to a technical or specific definition. I was using it to refer to small amounts of a substance in another. Our discussion so far has focused on

solvents, gasoline being a mixture of solvents. In a solvent mix, the percents we're talking about represent a small amount of benzene in that product. I don't think it is technically accurate to refer to it as trace if you're talking about trace as an analytical term.
Q. Okay. So the strict definition of "trace" would appear as an analytical, chemical word, or toxicological word and would refer to those amounts that you can detect but can't measure?
A. In a very strict sense, yes, but the word "trace" is also used in other contexts. For instance, "trace element" is used repeatedly to refer to small amounts of elements that are present in the diet and in the atmosphere and elsewhere. And in most of those cases, in many of those cases, you can accurately measure the amounts that are there. So it is used often to refer to small amounts of a substance which, if we're talking about its strict definition in an analytical sense, it means something you can detect, cannot accurately quantify.
Q. Okay. The way you just described, who uses the term in that way? What group of professionals would use it in that way?

A. Toxicologists, analytical chemists, environmental chemists.
Q. I'm not talking about the strict definition.
A. Oh, virtually anybody involved in environmental health or toxicology or nutrition.
Q. Okay. And the use of the word in that manner does not connote an actual percentage level that one would expect to find?
A. No.
Q. We're still on your list. Any other cases involve benzene exposure, Exhibit 2?
A. I believe Salazar Versus Ecolab was a benzene allegation.
Q. What was the exposure?
A. I believe it was occupational.
Q. Did you know what the disease was?
A. Chronic myelogenous leukemia.
Q. Do you remember what the exposure level was?
A. No.
Q. Where was that case pending?
A. Texas.
Q. Do you recall who the attorney was?
A. No.

Q. Do you know where in Texas?
A. No.
Q. Was it in the Beaumont area or-
A. I don't believe so.
Q. Okay. And any other benzene-related cases?
A. Taylor Versus Gulf may be a benzene exposure case, but I don't remember anything about it.
Q. You just remember that you testified in it?
A. I gave a deposition in that case. I don't remember who was involved or what the issues were.
Q. Okay.
A. Guidry Versus SmithKline, the allegation was benzene exposure.
Q. Okay. Have you testified in any other cases for SmithKline Beecham other than Guidry in this case?
A. No.
Q. Have you been consulted on any others for SmithKline Beecham?
A. I believe I have.
Q. Do you recall which ones?

A. A case called Cavanaugh.
Q. Were you retained as an expert in Cavanaugh?
A. I believe so, yes.
Q. But you didn't give testimony?
A. No.
Q. Have you ever worked for-- other than those three cases, have you ever done work for SmithKline Beecham before?
A. I don't believe so. I don't believe so. Certainly with respect to litigation I don't believe so.
Q. You may have done some consulting work with them though?
A. I don't think I have. I don't think SmithKline is a pharmaceutical company that I've consulted for.
Q. Have you ever done any work for Mr. Whitney's law firm before?
A. No.
Q. For any lawyers from Mr. Whitney's law firm?
A. I don't believe so.
Q. Any other benzene cases on the list? I know we're getting towards the end there.

A. Lavender Versus Miles.
Q. What kind of exposure was that?
A. it's occupational exposure.
Q. Have you testified in trial in that case?
A. No.
Q. Is there a trial date set in Lavender?
A. No.
Q. Do you know what the disease was?
A. It's leukemia.
Q. What type of leukemia?
A. Myelogenous, acute myelogenous.
Q. AML?
A. I believe so.
Q. Is AML considered to be one of the leukemias that is caused by benzene exposure?
A. Certain subtypes of AML can be associated with benzene exposure. That's correct.
Q. What types of-
A. Using the FAB classification, usually you're talking M1, M2.
Q. What is M1 and M2?
A. Mi would be acute myelodysplastic leukemia. M2 would be acute myelodysplastic leukemia with maturation. M4 would be myelomonocytic. M5,

rarely, if at all, would be monocyzic. M6 is erythroleukemia that has been associated with benzene exposure. M7 is basically, in the older terminolcgy, a myelofibrosis.
The information available on myelofibrosis is so scant one cannot say one way or the other, not only the morphologic subtype but also the cytogenetic subreport in evaluating the potential for causation associated with benzene, especially when you don't have-- when you either have evidence that does not suggest exposure or you have virtually no evidence of exposure.
Q. In what way are they cytogenetic?
A. (No audible response.)
Q. In what way are these cytogenetics important in an analysis of whether AML is caused by benzene exposure?
A. Secondary leukemias-- by that I mean leukemias that are the result of exposure to chemotherapeutic agents, radiation, or cohorts of which the only known cause is benzene present with a different pattern of distribution of abnormalities than one sees in de novo leukemias or those arising spontaneously with no previous history of exposure to benzene or chemotherapeutic agents.

Q. Are these cytogenetic abnormalities, chemotherapy, and benzene similar?
A. Yes. Yes, they are. Their use with respect to evocation is based upon differences in the pattern or incidence of their involvement in different leukemias that we're discussing. For example, if one looks at demonstrably clonal chromosomal abnormalities arising in AML, slightly over half of primary AMLs, de novo AMLs, will possess cytogenetic abnormality. Arguably, ninety-five percent or greater of secondary AMLs will possess an abnormality.
Q. So if, in fact, you have an AML, is the issue-- is it more likely than not that that AML is secondary or primary?
A. If there are no clonal chromosomal aberrations associated with it, it is more probable than not that it is a primary.
Q. The primary being non-exposure cases?
A. Yes.
Q. And in ninety-five percent of the exposure cases you're finding chromosomal abnormalities?
A. (Indicating.)
Q. Are these non-random abnormalities?

A. They tend to cluster to some extent, actually to a great extent.
Q. Where do they cluster?
A. Secondary leukemias, secondary AMLs associated with chemotherapy and with occupational exposure, show a very high predisposition for involvement in chromosomes 5 and/or 7. There are also others that are seen, but they're seen with equal frequency in both primary and secondaries.
Q. So primarily, when you do an analysis of this, you're looking for cytogenetic abnormalities surrounding chromosome 5 and/or 7?
A. Five or 7 certainly. Certainly 5 or 7 are seen together to a much greater extent in secondary AMLs than they are in primaries. In secondary AMLs they constitute together about-- it depends on the study, but somewhere between eighty and ninety percent of the secondary AMLs will involve 5 and/or 7 together. That's opposed to about fifteen-- ten to fifteen percent of primaries. So it is found with less frequency in primaries than secondaries.
Q. Seems like a pretty large difference?
A. It's a fairly large difference.
Q. Are the abnormalities you find-- what

abnormalities do you find in 5 or 7 in these types of cases?
A. Seven usually-- one either finds the loss of all or part of the chromosomes or both of them, one set. You almost never-- well, it would be incompatible with the life of a cell to lack both chromosomes, both 5's or both 7's, but one will see loss of 5, loss of 7, 5q-, which means loss of the long arm of 5, or 7q-, loss of the long arm of 7. In the case of 5, it's almost always an interstitial lesion if it's a loss of part of the chromosome.
Q. "Interstitial" meaning part of the long arm?
A. Yes. A specific region of the long arm.
Q. Which region is usually found?
A. 5q31 is the region that appears to be missing in the vast majority of cases.
Q. 5q31; 31 is a specific point?
A. Yes.
Q. On the arm?
A. Yes.
Q. And the range of deletion encompasses that point; is that-
A. Yes.
Q. Is there a range of deletion that you

find?
A. Oh, there's a wide range. One of the manuscripts I brought of mine reviews some of the recent studies conducted at the University of Chicago on that. One sees varying deletions from one case of AML to another.
But, if one looks at where they overlap, they overlap specifically in the region of 5q31. So that is the area that is deleted in virtually every case. But the range of deletions would vary depending on the individual.
Q. If you saw an individual with one of these deletions you've just described with AML, and there was evidence of benzene exposure, would your opinion, given those simple parameters, be more probably than not that it was caused by the benzene exposure?
A. If there was evidence of significant chronic benzene exposure, and you have an AML that with respect to its presentation and criteria fits the category for a secondary AML, the presence of clonal lesion of 5q or 5- would provide fairly strong evidence that there was a potential relationship. Basically what it says is that, if you have the parameters necessary to establish a link

between exposure to high levels of benzene or any other chemotherapeutic agent and AML that evolves with lesions that include 5, that is a pattern that you expect to see in the secondary leukemia.
Q. The leukemias, you've mentioned the subtypes of AML as being evidence that they're caused by benzene exposure or that they can be caused by benzene exposure. Is that evidence primarily epidemiological studies?
A. The evidence associated with secondary leukemia transcends the epidemiology that we have available on benzene per se. Certainly there are some collections of case reports and clinical presentations that provide description of the types of leukemias that have been seen in benzene. Although the studies aren't quantitative, they are generally consistent with what's been seen in the quantitative retrospective epidemiology that we have on benzene and in the cell specific epidemology that we have associated with benzene.
In addition to that, and I think just as important, we have a much larger literature that pertains to secondary leukemia associated with chemotherapy, in which we have a much larger base of information to characterize the biology of secondary

leukemias. Since leukemias are similar, if not identical, it provides a useful data base and literature for studying mechanisms of secondary leukemogenesis.
Q. The leukemias are similar, if not identical, in chemotherapy-related or treated leukemia?
A. Yes.
Q. And mutagenic or benzene-caused leukemia?
A. Yes.
Q. Correction. We won't use the mutagenic part of the question. We'll just leave it at benzene.
A. Benzene is not a mutagen. If what you're asking me is does benzene-induced leukemia fit a pattern that's consistent with what we see as alkylating agents, the answer is certainly. From what we know today the answer is yes. There are still some questions remaining to be answered that really relate to the weakness of the occupational literature in relation to benzene exposure, but in general it fits certainly and is consistent with what we see following chemotherapy.
Q. Would you consider the lesions in both

instances to be similar?
A. Certainly with respect to the molecular lesions that are seen, yes.
Q. When you say "molecular," do you mean the lesions occurring in the stem cell?
A. Lesions associated with chromosomes and with the genes that are involved and the processes that are involved that are associated with the regulation of growth and differentiation in blood cells.
Q. That would be the same for both types of the disease process?
A. I believe the literature supports that, and certainly our own research supports that.
Q. Okay. The epidemiology that you're referring to, I guess you were indicating that there are case reports, clinical reports, in addition to the epidemiological reports which all support the notion that AML and the variants that you've identified can be caused by benzene exposure. Is that-
A. In general, yes. The specific variants that are associated with secondary AML and chemotherapy are much better defined in the sense that we have many more cases. That is consistent

with what I've just described. In general, what's seen in occupationally exposed populations with benzene is consistent with that.
Q. Are you referring to the epidemiological reports?
A. I'm referring to both. The epidemiological reports, as I mentioned before, do not tend to provide you with as much detail on the FAB subtypes as do the clinical or the case collections.
Q. Why is that?
A. Well, the epidemiolgists have tended to lump things as opposed to separate them, primarily because it increases the power of their studies. If one is interested in causation hematology or biology, lumping is a very frustrating and uninformative behavior, because you can't distinguish one tumor type from another.
Recently, studies are attempting to analyze these data sets using specific information. That information allows us to look at specific leukemia type. We do not have quantitative information from epidemiological studies that allows us to go through the various subtypes and distinguish one from another with that degree of resolution.

Q. Is that partially due to the fact that most of these epidemiological studies are mortality studies?
A. The only-- I would say that question is-- if I answer yes to that, it's overly broad. One characteristic of mortality studies is that you're dealing with death certificates, which are obviously a fairly-- they're certainly-- they're reliable in the sense that they deal with mortality and you have a very specific input. Where they're not generally reliable is for a diagnosis at a level such as we're talking about. You're not often going to find a death certificate that says AML, FAB subtype M2. You'll see-- if you're lucky, it'll say AML. If you're not, it'll say leukemia.
So you are correct in assuming that an epidemiological study that uses mortality can often distinguish a leukemia class such as a CML or an AML, where it may be less useful in distinguishing the incidence of subtypes. That's where, as I said before, some of the collected case information is useful, even if it's not quantitative, because it gives you some idea of what the prevailing types are that have been seen.
And one can also look at, as I said,

the literature on secondary leukemias associated with chemotherapy, where you see a very strong and consistent patter, and it's consistent with what we have seen with respect to benzene.
Q. The death certificates also, I take it, would not show any kind of preexisting bone marrow toxicity condition that preexisted the AML or leukemias?
A. Not-- not necessarily. Not usually. You may have a secondary condition that's listed on a death certificate, but that's not always the case.
Q. Are most secondary leukemias preceded by a myelodysplastic syndrome?
A. Myelodysplastic syndrome is a frequent precursor to the frank development or clinical development of AML secondary to exposure to chemotherapeutic agents or benzene. Probably, depending on the study, myelodysplastic syndrome which used to go by the old rubric "preleukemia," preleukemia is included in that broader definition of myelodysplastic syndrome, forty to sixty percent, depending upon the study. Some people think it's higher. So when you say the majority of cases, I would say probably the majority of cases.
Q. Is it your opinion that virtually all

the cases of benzene-induced AML are preceded by a myelodysplastic syndrome if the data is available on those cases?
A. I would not be at all surprised to find the vast majority to have evidence of trilineage dysplasia, certainly some preceded by thrombocytopenia or lymphocytopenia leading to a trilineage dysplasia, and that evolving into frank AML, and that falls into the broader context of myelodysplastic syndrome. I would not be surprised at all to see that as the principal pattern that you would see in a benzene-induced leukemia.
Q. Were you saying trilineage?
A. Yes.
Q. What did you mean by that?
A. Involvement of at least three of the major lineages of blood cells, which is one of the criteria that one often sees.
Myelodysplastic syndrome is a relatively new term in that it became an officially accepted rubric, if you will, in the early '80s to cover a wide range of phenomena, some of which are related, some of which aren't, that are associated with dysplasias in the blood, blood-forming organs.
Trilineage dysplasia is one of the

criteria that is often used to describe a persistent myelodysplasia associated with preleukemia, and it's included within the definition of myelodysplastic syndrome for some of the categories.
Q. I take it then that the three major blood cells would be the platelets, white blood cells, and red blood cells?
A. There are certainly different lineages of cells, and you can break them down into different categories depending on what you're interested in. From the standpoint of the lineages that are involved when we talk about a trilineage dysplasia, we're talking about red cells, we're talking about platelets, we're talking about granulocytes, we're talking about lymphocytes. Those would be the major cell types that would be involved when we are talking about a trilineage dysplasia.
Q. Granulocytes and lymphocytes are white blood cells; is that right?
A. Yes.
Q. When you were discussing the q associated with AMLs, the leukemias, as being an indicator of potential benzene exposure for toxicity, is that something that you've learned through literature review?

A. I wouldn't call it an indicator of benzene toxicity. It is certainly a frequently observed abnormality in the context of secondary leukemogenesis and myelodysplastic syndrome that's associated with secondary leukemogenesis.
Q. Is that supported by the literature?
A. It's supported by the literature in secondary leukemogenesis, associated chemotherapy. There is no direct evidence that in fact benzene directly is associated with it, but I believe it to be so. In an occupational setting where you have exposure to solvents where benzene is the only leukemogen, you do see an increased frequency of 5q and leukemias that evolve in those individuals.
Q. When you said "direct evidence," what would that constitute?
A. Where benzene was, as part of the study, reliably demonstrated to be what the exposure-- what the agent was. In other words, studies that have looked at the involvement of cytogenetic aberrations in secondary AML tend to have fairly weak exposure characterization and use occupation or questionnaires as a surrogate for any information on what the exposure really was. Basically the weakest exposure data is

associated with studies that have the strongest cytogenetic information, whereas the stronger data is associated with studies that don't. So you can argue that the evidence for a direct role of benzene in 5q associated AML isn't there, but I do believe that it is. And certainly other experimental studies denote that benzene metabolites are capable of inducing aberration as well as several others.
Q. And your opinion is based on your own experimental studies?
A. To a certain degree, yes.
Q. And any other studies that your opinion is based on?
A. Yes. Those studies I mentioned with respect to solvent exposure and secondary AML as well as the prevailing pattern that's seen in the chemotherapeutic literature associated with secondary AML.
Q. Did you bring those articles with you today?
A. Some of them I did, yes.
Q. Which ones did you bring that support that view?
A. (No audible response.)
Q. Are these articles listed on your--

A. They're listed in-- I have a reference list for the articles that I brought today.
Q. Okay.
A. Probably the most expeditious way of doing this would be to look at two manuscripts I brought with me that I recently authored, because they summarize that data.
MR. WILLIAMS: Okay. Why don't we do this-- I need to make a quick phone call-- take a quick break.
(Whereupon, at 11:09 a.m., a recess was taken.)
A. The vast majority of articles I brought today deal with 5q- syndrome, which is a totally separate entity than what we've been talking about. And so that's what most of them deal with. There are a couple of articles I have written recently that summarize the secondary myelodysplastic syndrome and leukemia literature, and those are in here as well, and there are extensive summarizes of that literature base. I did not bring all that literature, because I-- my opinion deals with the issue of 5q- syndrome and not secondary leukemia in this case.
The two articles that summarize this

information: in detail are one that's entitled "The Process of Leukemogenesis" that's in press in Environmental Health Perspectives that I wrote.
MR. WHITNEY: Just so the record is clear, we might refer to the article, tab 19.
THE DEPONENT: It's tab 19. The other is tab 20, which is a draft of a book chapter that I've completed, again is Leukemogenesis As a Toxic Response. And those summarize the literature both for benzene and for chemotherapeutic agents.
Q. (BY MR. WILLIAMS)And those would be responsive to my question about literature-- about benzene causing abnormalities of the fifth chromosome?
A. That can be and that is associated with leukemias. Some of the leukemias that are found follow exposure to chemotherapeutic agents or benzene.
Q. Those are the two articles you just cited?
A. Yes.
MR. WILLIAMS: Let me look quickly through your book here.
THE DEPONENT: There is a bibliography in the front.

MR. WILLIAMS: Okay.
(Whereupon, there was discussion outside the record.)
Q. (BY MR. WILLIAMS) I want to mark the whole book as an exhibit, which would be Exhibit 3. In Exhibit 3 there's a reference list of cases. Are these the cases you're-- or the articles-- are these the articles you rely on for your opinions in this case?
A. As they are specifically directed to issues that I will present in this case, yes. There's a much larger literature base that I could or will rely upon that deals with other issues related to leukemogenesis, if in fact those particular questions are raised. This is what I had provided in support of my report and my opinions as I understand the issues to be in this case.
Q. Okay. I want to ask you some questions about benzene and how it affects bone marrow. Do you agree that benzene causes bone marrow toxicity?
A. Benzene can cause bore marrow toxicity if an individual is exposed to high enough concentrations for a long enough period of time.
Q. What is bone marrow toxicity?
A. Bone marrow is the major organ

associated with production of blood. That includes most of the white cells, certainly the immature -forms of all white cells, red cells, platelets. And toxicity to the bone marrow involves damage to the blood forming cells, either acute or subacute. That means transient damage, reversible damage, or irreversible damage, if in fact the insult is severe enough.
That leads to a decrease-- that can lead, in simple terms, to abnormalities in the production of blood cells, a decrease in various types of blood cell formation that results from altered regulation of growth in the bone marrow, or can lead to increase in proliferation in the production of abnormal types of blood cells, as you see in leukemias.
Q. How does the lesion occur which causes these various effects?
A. (No audible response.)
Q. Does a lesion occur?
A. Yes. Benzene in and of itself is not toxic to bone marrow. It has to be metabolized. Metabolism is a process of changing it chemically into other compounds. The body has a very extensive system for dealing with chemicals, because

we live in a world of chemicals. Food is made up of chemicals. We're exposed to chemicals every day. And we normally process these, and the body has a means of dealing with them. The overall goal is to eliminate them.
We metabolize compounds or change them into other compounds. Usually the strategy that's employed is to make them more soluble so we can excrete them. In the process of doing that, the body converts them to benzene, to phenol, and to polyphenolic molecules, hydroquinone being one of the major polyphenolic molecules.
In combination, these molecules, if you're exposed to benzene in high enough concentrations for long enough periods of time, leads to the production of these molecules and their distribution to bone marrow, where they're capable of producing damage to replicating cells primarily.
We know that benzene metabolites target cells that are dividing. And the major effects that these compounds have is in altering the process of division and the mechanics of how the cells come apart.
There are other changes that also occur that have recently been identified that suggest this

a characteristic of a variety of compounds, including benzene metabolites, is that they alter regulation of differentiation in the stem cell compartments, and therefore make these cells more susceptible to the types of damage that undergo a division.
Q. Is it your view that it affects the cell differentiation, the benzene metabolites?
A. It's certainly my view. There's demonstrable evidence, both from my standpoint as well as others, to indicate that that's the case. The precise nature of the mechanism of that is not completely understood, and we're rapidly studying it now.
Q. Did you bring the hematology study as part of the notebook? And you can identify it by tab number, if you would.
A. Some of these studies speak to the issue. A review of it is provided, a simplified review is provided in number 1, dealing with metabolism per se.
The role of metabolism is very important in benzene toxicity, and it's requirement in benzene Toxicity is a generally accepted tenet of the field. Tabs 20, 21, 22, 23, 24, 25 deal variously with benzene and the effects of

metabolism. They also reference other papers that deal with the specific mechanisms that I've been discussing.
I've recently proposed, for the sake of generating research and discussion, a model, one model for a proposed mechanism for the development of leukemia associated with benzene exposure. And that's summarized in 19 and 20.
Q. Are these the two other articles, that you had mentioned?
A. Yes.
Q. These are the ones going to press now?
A. Yes.
Q. Just a quick aside. Are these articles, all the other articles that have been published, are they all peer reviewed articles?
A. Yes.
Q. Is peer review an important concept in evaluating an article?
A. Yes. It's not the be all and end all, but it's a very important concept in evaluating a priori the value of an article with respect to being able to rely on its contents.
Q. What does peer review mean?
A. Peer review is the process of

independent review of the information design, experimentation design, and interpretations proposed in the paper by colleagues that is a part of the publication process that scientific journals require for publishing an article in a given journal.
So, if you submit a paper which represents the product of research or evaluation of data to a journal, the editors of the journal will submit it to independent reviewers to ascertain whether or not the collection of data, experimental design, and scientific interpretation of the data that's presented is, in fact, appropriate and valid. And that's one of the major processes for determining suitability for publication.
Q. Have the items at tab number 19 and 20 been peer reviewed yet?
A. Yes. Yes. When I say "in press," that means that they've been accepted for publication. Nineteen is a strict peer reviewed article. Twenty is a book chapter. I am presenting it primarily because it summarizes a lot of the information that we were talking about earlier that I haven't provided. It's been peer reviewed to the extent that it's been reviewed independently by an editor who has deemed it

acceptable. It has not received-- it is a book chapter. It does not have the same weight with respect to peer review as the other individual articles do.
The book chapter is useful for summarizing a great deal of information and for obtaining some idea as to what the state of art in a given field is, if you want to determine that. If you want to rely on something for reaching a scientific opinion, it's much more preferable to then go to the primary literature on which the chapter is based and review it yourself to determine whether or not the information that is summarized is in fact-conclusions of the author are valid. So book chapters are useful. But they are secondary sources of information, not primary.
Q. Okay. Back to the discussion we were having on metabolism. Is there more than one step involved in metabolism?
A. (No audible response.)
Q. Does metabolism occur more than once with regard to benzene?
A. Yes. Yes. Primary metabolism occurs in the liver. That results in the production of phenol. It results in the secondary production of

hydroquinone, some polyphenolic molecules. These are then subjected to further metabolism in different organs.
In bone marrow, myself and my laboratory and others have demonstrated, as a characteristic of the cells, that cells that are the precursors for development of acute myelogenous leukemia, the leukoprogenitor cells, have a particular pattern of metabolic capability that makes them susceptible to further toxicity by being able to further metabolize in particular the quinones to toxic molecules that are capable of interfering with cell division by binding to microtubles and the spindles that are associated with pulling the chromosomes apart during division.
Q. Is there a-- what occurs in bone marrow if there is an interruption of cell differentiation by the benzene metabolites?
A. Benzene metabolites appear to facilitate or increase differentiation down the myelo pathway, and what we think this is associated with is an increase in proliferation in the compartment of cells that are, in fact, the ultimate targets for the development of acute myelogenous leukemia. And anything that increases replication in a target cell

population presents a potential risk with respect to a permanent genetic alteration, in this case aneuploidy.
The first evidence that has been associated with the evolution of leukemogenesis and secondary leukemia involves the loss of all or part of a chromosome. That's the first permanent event. It's not the first event in the process. There are then any number of subsequent events that have to occur that are independent before even one gets to either myelodysplastic syndrome or to leukemia. But it's certainly the first event that has been documented to occur.
Q. Aneuploidy?
A. Yes.
Q. Is there a clonal aberration that occurs in the metabolic process?
A. The metabolic process can lead to a clonal aberration. That is basically the premise on which the model that we proposed is based. As I said, if you look at what benzene metabolites do, they are very efficient at disrupting the mechanism that's evolved in the separation of chromosomes. They're very inefficient at acting on DNA. But they're very efficient at the process of disrupting

the proteins that are involved in the separation. of chromosomes during division.
Q. What is the clonal aberration? Can you define what that is?
A. The first clonal aberration that's been associated with secondary leukemias appears to be either the loss of all or part of chromosome 5 and/or 7. One certainly can't exclude 8, trisomy 8, which is basically an addition of a chromosome. All are included under the rubric of aneuploidy. This appears to be the earliest event. It could best be described as necessary but not sufficient for the evolution of leukemia and is only the first stage in the process.
I have proposed a model which, as I said before, I think is architecturally sound, but would probably be subjected to further modification as we learn more, that I proposed last year. That's associated with -- it's in this paper. And I chose 5 in this model, primarily because we know about genes that are associated with 5. Seven is more frequently involved probably. But if one is-
Q. Are these growth genes that are associated with chromosome 5?
A. Yes. There are various hypotheses for

what is associated with that lesion. I happen to think that the growth genes are probably fairly important, the cytokine genes, with respect to the process that they involve. But there are other hypotheses that have been promulgated as well. This is the model I put forward.
Q. We're looking at page 27 of tab 19?
A. Right. I have to say this basically represents a hypothesis based upon facts that are known with respect to the evolution and process that's involved in the induction of AML secondary to chemotherapy primarily. But, as I said before, we do know that benzene metabolites can produce some of the same effects. We're looking at a progression. What this illustrates is a process that's now fairly well known in cancer biology, and that is that, for the vast majority of cancers, there's not a single event that's associated with the development. There are multiple independent events. There are multiple genetic pathways that can get you to the same place.
For example, if we look at-- we take chromosome 5, for example, chromosome 5 has been implicated as being involved in colon cancer as well. Now, that has no relationship to AML, but does

play an early role in the evolution of that disease. But, again, multiple independent genetic steps, some of them are genetic, some of them a=a epigenetic that have to occur before you get to the development of cancer.
Q. Well, on page 24, this process leads to carcinoma, and it is a 5q loss. Is that something you consider to be induced by the chemotherapy or benzene?
A. No. No.
Q. Is there a presumed cause of the loss in this model on page 24?
A. Cell division.
Q. Cell division?
A. Cell division is an inherently risky process. That's where aneuploidy occurs. In bone marrow we know, for instance, that ineffective erythropoiesis accounts for upwards of twelve to fifteen percent of the replicating blood cells in the bone marrow. During normal replication of red cells we have aneuploidy occurring. Most of the time it occurs in cells that are irrevocably committed to differentiation. The worst thing that can happen is they die, they disappear.
If it happens in an earlier cell that's

capable of clonality or clonogenic potential, then you may, in fact, have a spontaneous lesion occurring that leads to chromosomal-aberration such as 5q-. These are stochastic, random events. These are stochastic, random events even during the process of chemical leukemogenesis.
There's a constellation of several types that can produce or increase the potential for that type of injury, increase the frequency of those events. The events are still random. It's that their frequency has been increased in the case of colon cancer.
There's no-- with respect to the involvement of these molecules, this is the result of studies done by a number of investigators, this particular model that has been published by Harold Varmus and Robert Weinberg, based upon some very fine work by a variety of different investigators. It simply shows the fact that there are multiple ways to get to the same place, and there are multiple pathways involved. Some genes occur-- are involved early in the progression of the disease. Some genes occur later.
And the model that I proposed, a working formulation for secondary leukemia, is

architecturally similar.
Q. Back to page 27. You indicated earlier that the-- are there-- do the aberrations caused by benzene metabolites affect all the blood lineages?
A. If you're talk-- well, certainly the information we have on benzene and bone marrow toxicity does not suggest that it has a random effect on all lineages. For example, one of the papers I presented by Leon Goldwater and Greenburg from the '40s, I think, illustrates a finding that's consistently seen throughout the literature with respect to benzene and is actually seen to be consistent in animal studies as well. Chronic exposures to high concentrations of benzene can produce bone marrow suppression. But what one eventually sees is a thrombocytopenia, decrease in platelets, or a lymphocytopenia that occurs that precede any permanent effects and are associated with high-level, repeated exposure, chronic exposure. You may see some changes associated with anemia, but those usually actually follow thrombocytopenia or lymphocytopenia.
Curiously enough, the granulocytes are usually well resolved in benzene, and one usually sees a decrease in lymphocytes and a decrease in

platelets without a marked effect on granulocytes until fairly late in bone marrow suppression or toxicity. You can resolve that in asplastic anemia, in which you have a generalized inability to produce anything. But usually what you see early on in benzene toxicity involves lymphocytes and platelets first, and granulocytes are reduced much later in the process.
Q. And would you also see refractory anemia in such a process?
A. I couldn't characterize it as refractory anemia, certain not RA as it's found in the FAB classification. You usually see a trilineage dysplasia. You usually see-- you may see some aspects of a macrocytic anemia, but it's certainly not the first thing you see. And you usually see trilineage involvement. You don't see a classic refractory anemia as defined by the FAB classification.
Q. Would that be one of the things you might, see?
A. Well, a refractory anemia has certain characteristics that are included within the constellation of findings that I'm talking about. And refractory anemia in and of itself would not be a

pattern that you would expect to se` consistent with benzene exposure. You usually see, as I said, multiple lineage involvement.
Q. By that you mean reduction of red blood cells, white blood cells, and platelets, for example?
A. Not all white blood cells. I would expect to see a sparing of granulocytes, for instance. Refractory anemia is not consistent with the early effects associated with benzene poisoning. There are aspects of refractory anemia that are seen.
Q. Which aspects are seen?
A. One can see or it certainly has been reported that one can see macrocytic anemia, but this usually follows reduction in platelets and lymphocytes. Those are usually the most sensitive cell populations in humans.
Q. What study says that, that the macrocytic anemia follows a reduction in platelets and lymphocytes?
A. There are a number of experimental studies that suggest that. I reported that in the early '80's. The Goldwater/Greenburg work looking at industrial workers in New York in the late '30's, the mid to late '30's, suggests an absolute

lymphocytopenia.
Q. What are some of the other effects of benzene toxicity?
A. (No audible response.)
Q. Would pancytopenia be an effect?
A. Sure. Pancytopenia is basically one of the diagnostic criteria in the diagnosis of aplastic anemia.
Q. And would leukopenia?
A. Leukopenia simply represents a decrease in circulating white cells. Leukopenia is by definition something you'd see associated with pancytopenia. What's important is the cell types involved and the degree of suppression one sees. Leukopenia will occur in a number of situations that don't necessarily have to represent persistent injury or toxicity to the bone marrow per se.
Q. And one would also expect to see cytopenias?
A. Same thing.
Q. And the ones we've just been discussing?
A. Cytopenia refers to a specific cell type.

Q. How long has it been known that benzene causes those effects?
A. Certainly following high-level exposure to benzene it's been generally understood since the late '30s, early '40s.
Q. Was it postulated prior to that, as early as the 1890s?
A. Yes, following high-level exposure to benzene. But at the particular point in time where those studies were done we don't know what the cells were.
Q. What other effects would you expect to see that we haven't discussed yet?
A. With persistent exposure you're going to see either a hyperplastic or a hypoplastic bone marrow.
Q. A hypercellular bone marrow?
A. Either hypercellular or hypo, reduction.
Q. Okay.
A. If, in fact, one proceeds on to what is-- this is usually after many, many years subsequent to initial exposure, many years-- you may, in fact, see that type of presentation. If you do, and it proceeds on to a persistent abnormality,

trilineage abnormality, that would be classified certainly within the context of myelodysplastic syndrome. Within a pattern of a few months to a year or so, you have a very high likelihood it'll proceed on to the development of acute myelodysplastic leukemia or myeloleukemia, AML.
Q. And you mentioned thrombocytopenia as something that would be caused by benzene toxicity?
A. Yes.
Q. Which refers to low platelets?
A. Very low platelets. And that can be seen transiently. That can be a transient effect associated with repeated exposure to high concentrations over a short period of time and may be totally reversible, or it could also be consistent with multi-lineage involvement and a persistent involvement that continues after exposure ceases. These characteristics are not unique to benzene in many respects. They're found with agents that are toxic to bone marrow, the greatest-- the most potent of which are among agents that are routinely used in chemotherapy.
Q. And I take it MDS is also something that's caused by one of the effects of benzene toxicity?

A. Myelodysplastic syndrome is part of the continuum that's seen associated w_=h the development of leukemia secondary to exposure =c benzene or other leukogenic agents. In that context it is part and parcel of the process. But that's a small fraction of the total dysplasias that are seen that are classified within the rubric of myelodysplastic syndrome.
Q. I'm sorry. What is a small portion of that?
A. Most diseases that are associated with myelodysplastic syndrome are primary, spontaneous. They have a different prognosis, different characteristics. But it certainly is part of the process that's associated with the development of secondary leukemia.
Q. Essentially then, word you say that these various manifestations of the disease process are united by functional abnormalities in the growth in the blood precursor cells?
A. Yes, they are. To the extent-- and one can-- if one looks at the potential for evolution of anbormality or for the evolution of disease, they appear to be characterized as a part of that process as well. They have often the potential for further

development and evolution of myelodysplastic syndrome into AML, and to progress and to transform is a function of the number of abnormalities that are seen.
There's a very high frequency of transformation in myelodysplastic syndrome into AML in individuals that have more than one abnormality, very low frequency of transformation in individuals who only have a single abnormality. Secondary bone marrow toxicity, the evolution of AML tend to involve multiple channels, which is comparable to-- which is basically mirrored in the model that I showed you.
Q. On page 27-
A. Yes.
Q. -- of tab 19. I believe you have MDS listed in the model?
A. Yes.
Q. Would you characterize this as being a continuum of the disease process, starting with normal blood production, which is the hemopoiesis, then an insult to the bone marrow; then would that turn the continuum to leukemia?
A. In the context of secondary leukemogenesis, it is meant to represent one pathway that is both plausible and probable in the evolution

of secondary AML.
Q. I want to make sure I understand the pathway. How many pathways are there?
A. Well, as I said before, they are probably multiple. Certainly there is strong evidence to suggest that multiple independent pathways can get you to the same place for a variety of different tumors, including leukemia.
Q. Okay.
A. The only exception is probably CML, which is probably related to a single early event, although later events in the history and actual history of the disease are probably multiple as well. But for AML there's certainly multiple pathways.
Q. This pathway described on page 27, can you describe what that pathway is?
A. In general detail I can't. I mean this was presented basically as a straw model for' discussion and to generate experimental approaches to determining the evolution of the disease. Basically what it refers to is that, as I said before, the earliest permanent event involving a change in the genetic material appears to be the association of a loss of chromosomes, all or part of

chromosomes. Seven is most frequently seen.
I did not pose a model to 7, because
7-- we have a bunch of addresses for genes on 7, but
we don't know what they are.
Q. So your model is 5q-?
A. So I've chosen the model as all of or
part of chromosome 5.
Q. Let me interrupt you and ask you-- I'm
not trying to be rude-- I just want to make sure I
fully understand. Earlier you said benzene was not
mutagenic, but you're saying that it disrupts the
genetic process?
A. Benzene metabolites are clastogenic.
Q. What does that mean?
A. Well, to a large extent-- this is a
semantic argument, but to the extent the semantics
that are used can be confusing, I think it's
important to distinguish between the two.
"Clastogenic" means that benzene metabolites, as I
have discussed them, are capable of causing
chromosomal damage, they can cause a loss of
chromosomes, they can cause aneuploidy.
What's involved specifically in the
interstitial lesion of the segments of the chromosome
nobody really understands. But I think that

certainly, as benzene metabolites are capable of inducing aneuploidy and the loss of chromosome 5, whether it's possible to cause interstitial lesions is not that important in understanding the evolution of leukemogenesis.
Having said that, the point is that is a separate type of event from the binding of a molecule to DNA, which can lead to a misreading of the DNA code, and that's what we normally think of as a mutation or mutagenesis.
In the early days of cancer biology, especially from a regulatory point of view, because we don't know much about cancer at all, regulatory for purposes of standard setting, regulatory policy was to assume that there was no threshold for cancer genes and that they acted through binding through DNA. They caused a mutation. A single molecule of a single strand could bind to DNA, alter the code, and that would cause cancer. That is no longer a generally accepted tenet, and it, in fact, in many cases has been demonstrated to totally misrepresent what we see in the evolution of cancer.
The colon model I presented in this model here for AML illustrates that. We're talking about multiple independent events. The first one

that we've been able to identify in a variety of diseases has to do with chromosomal loss, not with a point mutation, a so-called mutagenic event.
So when I talk about benzene not. being mutagenic, there are two issues here. One, benzene itself isn't mutagenic or clastogenic. It requires metabolites, but beyond that benzene metabolites do not tend to be very effective interacting with DNA, i.e. mutagens, but they're very potent together. They form a very potent capability for disrupting cell division and causing events that can lead to aneuploidy.
Q. Would you characterize that as a nondysfunctional event?
A. Yes.
Q. Which can lead to chromosome breakage?
A. Yes. Or causes chromosome loss.
Chromosome breakage is another story. We have a lot to learn before we fully understand that.
One of the reasons why I say that is, for instance, if you take 5q-, almost all of us, no matter what the age is or whether there's no aging involved and we're talking about spontaneous deletion of part of a chromosome occurring obstensibly as a division accident, you see the interstitial division

at 5q. So the 5q- is not always but almost always an interstitial deletion. Whether that 1--as chemical specificity is totally conjecture.
Q. You've been describing the continuum of the disease process?
A. Yes.
Q. You don't have a lot of the things we've been discussing on here-- maybe you do in broader terms-- but, if I give you a piece of paper, can you draw the continuum of the disease process occurring after a lesion to bone marrow caused by benzene metabolism?
A. (No audible response.)
Q. Does that make sense?
A. No. I'm sorry.
Q. Why does that not make sense?
A. These are stochastic events.
Q. What does that mean?
A. They're random. By this model, which again is a model for generation of research and discussion, architecturally it would probably withstand the test of time. But when the individual events on the spectrum end up remaining as they are, the explanation of what they do is going to require a lot more research.

So I'm not pretending to tell you that this is how AML occurs. And _ can't draw you a road map that tells you exactly what molecular events are transpiring.
We do know that agents that are leukemogens, and that includes benzene metabolites, are capable of altering normal differentiation in the stem cell compartment. Now, ostensibly that alteration leads to increased hypersensitivity-- is a good word-- to growth factors, specifically GMC.
Now, that's going to cause an increased number of cells that are responsive to the growth factor and are dividing. That by itself is transient. It's not permanent. It has a window that probably is on the order of hours, during which time you have more cells dividing in the target cell compartment than you would have otherwise.
The system has naturally evolved to protect us from that kind of injury. So, for instance, an agent that simply causes chromosomal damage that are compounds that we know will cause bone marrow supression that can cause aneuploidy that are not leukemogens, probably not leukemogens, but they probably do not alter regulation in the stem cell compartment. And that may, in fact, alter the

number of target cells available for further damage.
Now, you can then incur the loss of a chromosome. In this case I've used 5. We know benzene metabolites in culture will cause 5-. No evidence they cause 5q-. Certainly they cause 5-. They cause 7-, 8-. They cause a random array of chromosomal aberrations.
But what you end up seeing that persists during the evolution of AML are those that appear to be important with respect to the evolution of the disease, and 5 is of one of them.
Q. 5q- would be one of them?
A. Yes. From what we know is going on at that location on the chromosome. And it makes sense that it would be involved in this process.
Q. Are the studies you're referring to animal studies?
A. No. These are studies involving human cells.
Q. Human cells?
A. Human cells in humans with AML. Animal studies, with respect to looking at specific chromosome loss and gene involvement are irrelevant, because the genetic mapping of genes and their location on chromosomes in animals are different than

in humans. And if one wants to look at the propensity for involvement of specific chromosomes and genes in the evolution of human cancer, you have to look at human cells.
Q. How many of your studies have looked at human cells?
A. Well, I think that probably depends on what you call a study. If we're talking about-
Q. I'm going to pull this out, because we might refer to it.
A. You're talking about individual publications at this point in time. I could probably give you a number. The fact is the work that we've been doing for the last seven, eight years has been largely devoted to looking at these processes in human cells.
Q. What you say "we," who are you referring to?
A. My laboratory.
Q. At the University of Colorado?
A. University of Colorado. Now, one can look at processes. One can look at individual events using animal models or animals cells as models. But, if one wants to integrate them into a cogent model for the evolution of a disease such as AML, you have

to basically look at the human gene and the organization of genes as they are found in human cells, not in animals cells.
Q. Have most of your studies been animal studies?
A. If you look at my whole-- in my record over the past twenty, twenty-five years, yes, most of the work has been in animals. We've only recently developed-- by recently I mean the last ten years- the techniques to begin to directly look at human cells.
In humans, what we've seen over the last few years is virtually an explosion in terms of our knowledge of mechanisms associated with hematopoiesis and development of leukemia and cancer.
Certainly hematology, I would say that eighty percent of what we know today we've learned in the last ten years, maybe five years, with the exception of clinical description of diseases, clinical, laboratory, traditional morphologic techniques. What we know about the mechanism of genesis, the vast majority of our knowledge we've gained in the last five years.
Q. You have your resume in front of you?

A. Yes.
Q. Which one of your studies on there were human cell studies related to benzene toxicity?
A. Well, certainly the European Journal of Haematology, Environmental Health Perspectives, in Press.
Q. Are you talking about articles now?
A. Yes. I don't know how you want to do this.
Q. Why don't you identify the page number of your CV?
A. Page 10.
Q. And you can just read the title of the article.
A. "The Effects of Benzene and other Leukemogenic Agents on Hematopoietic Stem and Progenitor Cell Differentiation" is human. "A Epidemiologic Study of Benzene's Early Biologic Effects in Heavily Exposed Workers in Shanghai, China" is obviously human. "The Process of Leukemogensis," 1966, is human. "Impact of Benzene Metabolites on Differentiation of Bone Marrow Progenitor Cells" is human.
"Dideoxycytidine-Induced Thymic

Lymphoma Correlates with Species-Specific Suppression of a Subpopulation of Primitive Hematopoietic Progenitor Cells in Mouse but not Rat o= Human Bone Marrow" deals with human.
"Peroxidase Activity in Murine and Human Hematopoietic Progenitor Cells: Potential Relevance to Benzene-Induced Toxicity" deals with human.
Those are the current papers that I have that deal directly with looking at the effects of benzene and other leukemogenic actions or leukemia agents in humans.
Q. And did any of those studies determine that benzene metabolites caused damage to the fifth chromosome?
A. No. We're currently conducting those studies. I'll probably be ready to publish that information. within a month or so.
Q. Is there a point at which benzene, the metabolism of benzene, becomes saturated?
A. Primary metabolism is probably saturated at about one hundred parts per million, maybe between one hundred and three hundred parts per million. Secondary metabolism is probably saturated somewhere within that range. But we don't completely

understand that.
Q. So the only one you have an opinion on within a reasonable degree of medical certainty-or scientific certainty is primary metabolism as to the when-
A. When saturated?
Q. Yeah.
A. Yes.
Q. What does it mean to say it's saturated?
A. It means that basically you have maximized the process, and there is no increase in the rate of transformation of molecules that can occur by increasing the concentration.
Q. And does that mean that the amount which is absorbed above that saturation point is not going to be metabolized?
A. Essentially, yes.
Q. So, if someone inhaled air or was exposed to benzene in parts per million which exceeded a hundred, the amount above one hundred parts per million would not be metabolized; is that a fair statement?
A. No. The rate of transformation of benzene into the metabolites will not increase. You

basically will then have a constant rate of formation of primary metabolites. Doesn't mean that secondary transformation or tertiary transformation, which are just as important with respect to toxicity, will not continue to occur.
Q. But, as of today, we don't know that?
A. I think we do know that. We know that it occurs. We just don't know precisely what the saturation is for cell specific production of individual metabolites under those circumstances. Whether or not saturation occurs is really not all that important. I think that's an overly-- I think there's too much attention paid on saturation. It's important for pharmacokinetic modeling, but it doesn't, I think, give you a great deal of information with respect to potential toxicity.
Q. Well, with regard to primary metabolism, if a person is exposed to amounts over one hundred parts per million, will that excess amount pass into the body unmetabolized, or is there a percentage that you can say will pass into the body unmetabolized?
A. Yes. And, as a matter oz fact, it can happen at lower concentrations. You don't have to

reach saturation with a compound that can be spontaneously excreted.
And benzene is volatile. And the primary route of excretion of benzene is through the lung, inhaled. And so, in a situation like that, you're going to see excretion of benzene at concentrations below saturation.
Q. The primary route of excretion for any level of benzene is through the lung, unchanged?
A. No.
Q. If it's inhaled?
A. No. In a very, very low concentration, the primary route of excretion is going to come from excretion through the urine or the feces, primarily the urine. A higher concentration, at some point- it's incompletely understood, but generally well recognized-- exhalation of benzene becomes the primary route of excretion. But-
Q. What approximate point is that?
A. Certainly above a hundred and probably somewhere, I would say, around fifty you begin to see it lipping up. But the fact of the matter is you can measure benzene readily in exhaled breath of individuals.
In smokers it's quite high, and in

individuals with no exposure to benzene you can still measure benzene excretion via the lungs. So there's benzene in your breath right now. It can be measured.
Q. So at fifty parts per million exposure you would start to see larger percentages not metabolized of the benzene?
A. I would expect so, yes.
Q. And after one hundred parts per million?
A. You've reached a point where any benzene taken in, the major increase in its fate or the major-- its major fate will be exhalation.
Q. At some point I take it. Okay. Is there a percentage? Is it ninety percent-
A. It depends. I would suspect that above one hundred parts per million you could be talking as much as eighty percent. But I mean these numbers are by no means hard and fast.
Q. But, if you were around eighty percent, you would expect to see at one hundred and above which would be excreted unmetabolized?
A. Yes.
Q. Then I take it that goes down, that percentage that's excreted unmetabolized decreases as

you get closer to the saturation point coming down the scale, and then get below the saturation point; is that a fair-
A. It is. But I mean these are-- it's not that simple. If you're talking about mass balance; that's true. But, as I mentioned, even as ambient levels of exposure to benzene that occur every day, there is benzene excreted unchanged via the lungs.
Q. Even at background exposures?
A. Yes. It's been demonstrated. The EPA has measured benzene in the breath.
Q. Well, if it's in someone's breath, they must have been exposed somewhere, wouldn't you say?
A. Sure. Everybody is, every day.
Q. So let's take, say, ten parts per million, air concentration; would you expect to see most of that benzene metabolized?
A. Ten parts per million, probably, yes.
Q. And I guess-- would that hold true for one part per million as well?
A. Yes.
MR. WILLIAMS: Take a one-second break.
(Whereupon, a document was marked Irons Deposition Exhibit 3 for identification by the

reporter.)
Q. (BY MR. WILLIAMS) Is the metabolism of benzene the same in all species?
A. Qualitatively, probably so. There certainly aren't any major differences that have come to light, although there could be some minor difference's.
Q. Are there any studies which would support your view that the metabolism is the same?
A. Many. There's certainly no appreciation in the literature related to benzene metabolism that humans have a different pattern of metabolism: The cell specific metabolism is probably much more important than overall metabolism in terms of conferring susceptibility, and there you do see differences.
In rats the target organ for benzene is the Zymbal gland, and in mice one sees toxicity in a gland called the preputial gland. And one characteristic of human bone marrow, the Zymbal gland and preputial gland, is the concentration of myeloperoxidase, which is known to be a very important enzyme in the terminal oxidation. of hydroquinone.
- Recent studies in humans suggest that

also a detoxifying enzyme called DT-diaphroase or NQ01 is an important enzyme in benzene toxicity. Its absence in the bone marrow of humans, polymorphisms in the gene that's associated with NQ01 appear to be correlating with benzene toxicity in studies that are ongoing in China and elsewhere.
Q. Have you cited these human studies in your list of articles that's included in Exhibit 3?
A. No.
Q. And these are not studies you have participated in?
A. Yes. Some of them aren't, and some of them are. One of the articles that I do cite here is where it was demonstrated that, in fact, peroxidase is found in the hematopoietic progenitor cells in humans. And much of this work has been conducted at the University of Colorado, either in my laboratory or that of Dr. Ross, who has been actively looking at polymorphisms associated with DT-diaphroa se as well.
Q. Has the metabolism of benzene been studied in liver cells in vitro?
A. Yes. Yes.
Q. By you?
A. In the past I've participated in a number of studies that would look at in vitro and in

vivo metabolism of benzene. I haven't done any liver work in many, many years.
Q. When was the last time?
A. It was when I was at CIIT. It would have been the late '70s, early '80s.
Q. Benzene is primarily in humans metabolized in the liver; is that-
A. Primary metabolism is the liver, and that's humans, mice, rats, virtually all species that have been examined.
Q. And we're talking about animal studies now. Are these animal studies important in or useful in understanding the metabolism process of humans?
A. Yes.
Q. So the results of these animal studies would be extrapolated to human subjects?
A. Animal studies are extremely important for understanding individual processes, when you're talking about metabolism or toxicity. The problem with animal studies is there is no animal that is a complete and total surrogate for humans. So you can extrapolate, you can compare, you can reach conclusions that are based upon experiments in animals, but you have to be able to validate the major tenets of those conclusions

using human material or analogy to human studies, the point being you can extrapolate many aspects of processes that are 4nvolved in metabolism of benzene to humans.
If you want a model for the pharmacokinetic modeling of humans, you have to use some human material co fill out the picture. You can't simply take a mouse or a rat and say this is a small human and directly use that data to predict precisely or quantitatively what will happen in humans.
But pharmacokinetic-- physiologically based pharmacokinetic models made extensive use of animal materials. Uses in vitro human studies as well to fine-tune and test the parameters and the results that are seen from the animal studies and then produce a model that predicts what happens in humans.
Q. And these in vitro studies would be with liver-
A. Some of them.
Q -- cells?
A. Some of them. I think the most important ones today with respect to understanding what's going on occur in bone marrow. We know a lot

about the liver process in all species. The liver is not where the terminal or endpoint of metabolism occurs that's associated with benzene toxicity. It's the bone marrow. So-
Q. Does a secondary, tertiary metabolism occur in the bone marrow?
A. Yes.
Q. Do you agree that benzene itself, without being metabolized, can have a toxic effect on bone marrow?
A. No, not at concentrations that are of any physiological relevance whatsoever. Benzene by itself is virtually inert until you get to concentrations that basically dissolve in liquid, and that's not compatible with life.
Q. Is that a subject of debate, whether benzene itself causes damage to bone marrow?
A. It has been, but I don't think it is now. It's been demonstrated. There are a number of different laboratories now that have not been able to demonstrate that primary metabolism occurs in bone marrow of humans. There have been studies that have looked at the effects of benzene by itself and have suggested it might have some effect on the process of influencing, but the concentrations of benzene that

were used are not physiologically relevant.
Q. Do the liver cells from different individuals metabolize benzene differently on a quantitative basis?
A. There's some evidence that the specific types of enzymes that are associated with primary- the specific enzyme associated with primary metabolism of benzene is an enzyme called QE1. It is an isotype or isoform of an enzyme. It's a constellation of enzymes that are called QE1, Cytochromes P-450.
There's some evidence that, in fact, there is some polymorphism in humans with respect to metabolism of a variety of compounds associated with cytochrome P-450 with respect to human toxicity. Humans tend to show less variability with respect to that process than various strains of rodents do. At this point the polymorphism that appears to be the most important in susceptibility, certainly associated with benzene poisoning in humans, is the enzyme I talked to you about before, NQO1, which has been associated with secondary detoxification. Now it appears to be-- polymorphism appears to segregate with toxicity, at least in studies that. have been done in China.

Q. That would indicate a variability in toxicity among individuals?
A. Sure. We've seen that. We've seen that in the benzene literature already. I don't think that's subject to discussion.
Q. That individuals vary in their susceptibility to benzene toxicity?
A. Certainly. If you take any population, even the Turkish shoe workers or Italian shoe workers that were exposed to egregious concentrations of benzene following World War II, where we had massive epidemics of benzene poisoning in individuals exposed to hundreds and hundreds of parts per million of benzene chronically, repeatedly, over and over, not just for eight hours but for twenty-four hours a day, we still only see a fraction of individuals that develop bone marrow suppression. We only see a subfraction of those that go on to develop persistent lesions, and even a smaller fraction of those go on to develop acute myelogenous leukemia. So clearly at concentrations that are toxic to bone marrow you only see a subset of individuals that get sick.
Q. And you attribute that to individual susceptibility?
A. Certainly, by definition.

Q. Is differences _n the way individuals metabolize benzene the only =actor that affects susceptibility?
A. I'm convinced it's probably a major factor. But, by the same token, I have spent a great deal of my time and effort looking at alterations and regulations of specific cells, at bone marrow function in humans, and I would not be surprised at all to find that there are some other differences that may impact on that.
Certainly to date we haven't seen any major ones. We certainly have not seen any major polymorphisms, if you will, with respect to the response of human bone marrow to benzene metabolites or to other chemotherapeutic agents.
But metabolism clearly is an area where there's likely to be an impact on susceptibility related to individual factors.
Q. What other factors might be important in that?
A. Other exposures, other behaviors, environments. I think smoking is likely to play a role.
Q. You mean life-style? Would you include it in the lifestyle category?

A. Lifestyle, diet, individual variations in stem cell differentiation and progression.
Q. Would that be a genetic concept, individual differences in stem cell differentiation?
A. Some of those-- certainly the ones that I think are the most likely hypotheses to date are environmental. But they remain to be tested. We are in the process of designing experiments, conducting experiments to look at the influence of smoking on that process.
Smoking increases white count dramatically. No one knows why. If, in fact, it's altered cell differentiation rather than a terminal maturation process or margination, it could readily influence a susceptibility to agents that target dividing cells.
At present I don't know of any, with the exception of defined diseases, where we know that there are processes that are abnormal to begin with and that are associated with various anemias or what have you. I'm not aware of any hypotheses that directly relate to genetically determined differences in, say, stem cell susceptibility.
Q. Would you agree that the genetic makeup of different people might enable some people to fight

off disease more readily than others?
A. It's almost -- well, the answer to the question is obviously yes. But that's like asking do you believe in mother and apple pie. I mean genetic makeup is all we are. All we are is a product of our genes. And we each have a different legacy with respect to the genes we've gotten. We interact with our environment.
So obviously our genetic makeup is important in influencing our susceptibility to the development of various diseases and our ultimate fate, whether we're destined to develop cardiovascular disease or colon cancer or what have you.
(Whereupon, from 12:51 p.m. to 1:08 p.m., a recess was taken.)
Q. (BY MR. WILLIAMS) Doctor, we've been discussing the initial insults to bone marrow that can be caused by benzene. And my understanding is that benzene metabolites can cause a lesion which leads to a disruption in cell differentiation. Is that a fair statement as the initial point in the process?
A. They certainly disrupt or alter differentiation. Whether there is a lesion or not

that's, I guess, a semantic question. It's a transient effect. It's temporal. It is probably- it's probably associated with changes in signal transduction from the surface of a cell to the interior and not with a genetic event. The first genetic event that is associated with-- that we know is associated with secondary leukemia development and with benzene metabolites, their chemistry is consistent with, is aneuploidy, the loss of all or part of a chromosome that then can lead to further alterations with time.
Q. So the first step in the process could be the disruption of cell differentiation, then a chromosomal abnormality or aneuploidy?
A. Occurring in that population, yes.
Q. Subsequent to those events, does there then occur a disease process that can eventually lead to AML, or have we already started the disease process?
A. No. The outcome is by no means fixed in time at that stage.
Q. I understand. Okay. At that stage what can happen? Can a person manifest symptoms of toxicity?
A. One looks at the concentration of

metabolites that are necessary to produce those events.
If one looks at chromosomal aberrations that occur in individuals following chemotherapy or exposure to benzene, it's clear that the levels of exposure that are consistent with that type of abnormality are consistent with some effect at the level of the bone marrow at that stage. One should- it would not be unlikely to see lymphocytopenia or a transient suppression in blood cells at that point in time.
Q. That would be no red blood cells?
A. Yes. Although you have to keep in mind that the half-life of red blood cells is very long in circulation. So if you have a transient effect that even involves exposure over a period of days, they're going to be much less-- red cells are going to be a much less sensitive tool than, say, for instance the lymphocytes, which have a much shorter transient period in peripheral blood.
Q. If a transient benzene exposure has caused these effects, is it possible that the effects will dissipate too on removal from the exposure?
A. The effects we've just talked about, yes.

Q. At what point do the effects become permanent and not removable or not curable by removal from the exposure? Can you even quantity that?
A. At this point in time, the development of permanent or persistent cytopenias, myelodysplasia, AML associated with exposure to benzene or any of the other agents that are known leukemogens, the precise dose duration product is not understood. It clearly represents a chronic event. We're talking about repetitive exposure that increases the likelihood that a permanent event will occur.
Now, when we talk about the progression or mechanisms that are involved in the progression of the development of AML, we're talking about events that happen in single cells. It's a rare event. Whether it leads ultimately to the evolution of leukemia is a stochastic process.
Q. What does that mean?
A. It's random, as I said before. Exposure can alter the frequency or the probability that that type of an event will occur. It does not specifically produce a selective event. So, if you have, for instance, a clone of cells that survive an exposure insult in which

aneuploidy has occurred and involves chromosome 5 and 7, that clone may persist for years. If it continues to divide and replicate, it may -- replication is controlled by interaction of those cells with their environment, which includes the stromal cells of the bone marrow and any other external factors. It's a regulatory process. That ostensibly is disrupted if you have lesions such as what I'm describing. As that begins to unfold, you may begin to see clinically or functionally processes-- a process developing such as myelodysplasia, dysplastic changes in the bone marrow, multiple cytopenias persisting. If that clone continues to evolve, you may-- you then have increased frequency of division or turnover occurring. And those cells are susceptible to other random events. Those events can involve endpoint mutations, loss of function of genes that change the biology of the cell. And that's basically the type of process that occurs in the evolution of a disease like AML.
Q. So no one knows at what point an exposure or duration will produce that exact effect?
A. Not precisely. We do have a lot of information with respect to the latency or the

duration of time that's associated between significant exposure to benzene and to onset of disease.
We know the types of and the frequency of manifestations of toxicity that are seen in many cases that then ultimately correlate with the evolution of the disease. But, with respect to whether or not a specific event at a place and time is going to lead to the evolution of leukemia, we can't predict on an individual basis.
So, even if an individual has clonal, chromosomal aberrations, there is no way of predicting what the chances are that he will go on to develop leukemia.
Q. Okay. Would continued exposure to benzene worsen the clonal aberration once it's formed?
A. I think you could make a much mc-e cogent argument that it would lessen. Between 1900 and 19-- possibly the end of the 1930s, actually benzene was used as a chemotherapeutic agent. It was used in the treatment of leukemia.
It's not very effective. It's fairly weak compared to most of the therapeutic agents that we have today. But it was used as a drug for the

treatment of leukemia.
If you already have a persistent clone that's undergone proliferation that is -rot regulated-- normally benzene's cycle specific and cytotoxic-- the same process that can lead to the evolution of the abnormal clone can also kill those cells. And that process is what occurs during the events that you see in acute benzene poisoning, where you have high-level exposure and you have transient effects in the bone marrow.
What benzene is doing is causing not dysjunctional events that lead to cell death. It's inhibiting lymphocyte proliferation at those concentrations. It's subsequent exposure is not likely to exacerbate the process. It's likely, if you have significant exposure, if it's going to do anything, it's likely to impede it.
Q. So, once the clonal aberration is present and persisting, the damage is already done in terms of the disease process?
A. No. That's the first-- that is one step in the process. There are now multiple steps that have to occur.
What I'm saying is that where benzene metabolites act is very likely to be early in the

process, not late. The types of effects that are seen are consistent with the earliest effects that are seen in the evolution of AML, not late effects.
Q. The effects we've been discussing earlier, the cytopenias and-
A. Yes. And the types of aberrations that are seen. The lesions that are associated with late events in the evolution of AML are probably at random and are governed by the rate of replication in the cells. Benzene can target those cells and kill them.
When I speak about benzene, I'm referring really to metabolites, not benzene itself. In that context, high-level benzene exposure, it's more plausible that benzene is going to impede the process, not exacerbate it.
Q. So would intermittent benzene exposure be potentially more damaging than chronic?
A. Intermittent is chronic. In an occupational setting or a setting where individuals are exposed to levels of benzene that are high level to produce bone marrow toxicity, you're almost dealing with intermittent exposure.
Q. By "intermittent" you just mean lack of completely continuous?

A. Yes.
Q. Okay.
A. Benzene is cycle specific. It's been known for years.
Q. Once you have this pathogenesis, once the lesion has occurred and the clone has been formed, the chromosomal aberration, what types of manifestations do you see at that point, or do they vary per individual?
A. The precise role of a given chromosomal aberration in the evolution of the disease is not understood. There are processes that are currently being studied. And there is a very-- there are some-- there's some evidence to support alternative hypotheses.
The best example I can think of is- let's talk about 5q-. In individuals who have solely 5q- and nothing else, no other chromosomal aberrations, the evolution to progressive myelodysplasia or transformation to AML is very rare, less than ten percent.
Q. So those occur in just those patients with just that chromosomal aberration; is that correct?
A. It can, yes. I said less than ten

percent. A small minority of those individuals can go on to develop-- to transform, yes. But the likelihood is that it won't.
That is a distinct population vis-a-vis other types of aberrations or multiple aberrations in terms of chromosomal aberrations. And it is also consistent with what one sees in terms of the findings.
5q- by itself is seen often in the aging populations. And that in that context it's associated with refractory anemia. And refractory anemia has cytoblasts. It has about a ten percent or less conversion rate to AML. That tends to be what one sees.
If one sees multiple chromosomal aberrations, say if instead of 5q- you've got -5,-7, or a combination thereof, or other potential aberrations as well irrespective of the origin of that lesion, you now have a totally different prognosis with respect to potential for evolution. Those individuals tend to have a higher rate of transformation, a much more rapid rate of transformation and progression of the disease, and a very high incidence of conversion to AML.
One also sees, instead of just seeing

the refractory anemia or macrocytic anemia-- one tends to see trilineage involvement. One sees what the FAB would call refractory anemia with excess blasts, increase in immature forms, lack of maturation.
Q. Which is the hypercellular bone marrow?
A. It's the hypercellular bone marrow in all of them basically.
Q. Would you see a lowering of platelets?
A. Well, trilineage involvement would mean a cytopenia very often involving platelets. In the case of benzene you usually see that early.
Q. And you'd also see leukopenia?
A. Which is part of the same. Leukopenia simply refers to a decrease in white cells. That would be due to a decrease in basophils or a decrease in neutrophils or both.
Q. So these various blood dyscrasias we've been discussing are part of the continuum of the disease process?
A. In the context of the evolution of secondary leukemia, secondary to exposure to high levels of benzene or other leukemogens, yes. In the context of spontaneous evolution of diseases such as the 5q- syndrome, no.

Q. Do you believe that 5q- syndrome is only spontaneously induced?
A. If you are defining 5;- syndrome, there is only evidence to support that it is a spontaneous lesion. If you are talking about tie evolution of involvement of chromosome 5, as in other diseases such as secondary leukemogenesis or colon cancer, it's clear that chromosome 5 can be involve4 in a variety of different disease processes.
I have seen nothing in the epidemiological literature associated with mechanistic study looking at mechanisms of leukemogenesis that would support the notion that 5q syndrome is the same thing.
Q. Is 5q- syndrome, as you're calling it, a form of bone marrow depression?
A. Ostensibly, yes. It leads to an anemia. It may lead to cytopenias of one type or another, often involving granulocytes. Again, that's a pattern you don't see very often associated with secondary leukemogenesis.
Q. What studies are you referring to that show that 5q- cannot be caused by benzene exposure?
A. First of all, I think it's misleading to characterize that as a scientist Dr science has

studies that prove a negative. Second of all, 5q-, if you're talking about the loss of the chromosome, I've already testified to the fact that I think involvement of chromosome 5 is consistent with secondary leukemogenesis.
If you're talking about 5q- syndrome, there is plenty of evidence to suggest that, with respect to origin, age distribution, prognosis, treatment, and characteristics of the disease, that it's a separate syndrome. I have brought with me several articles that indicate that.
Again, if you're asking me to point to studies that prove 5q- syndrome is not related to any type of exposure to benzene, the fact of the matter is science doesn't prove negatives. That's not something that we can do.
Q. What is the incidence of MDS?
A. It's variants dependent. The only quantitative study that I've seen which is consistent with certainly the clinical impression one sees in the literature is the study in Texas, which showed very clear age dependence.
The overall incidence age-adjusted is on the order of .006 per hundred thousand. The incidence in individuals 20 to 29 is on the order of

about that. No. The overall incidence is two to 2.9.
In the second decade of life it has an incidence of about .06. With age it goes up dramatically. In the seventh decade the incidence is on the order of twenty per hundred thousand.
Q. Twenty per hundred thousand?
A. Yes.
Q. How many people did you have to study to show a significant increase in the incidence of MDS?
A. It would depend on the population you're talking about. If you're talking about the second decade of life, where the incidence is extremely low, one would have to-- I can't do it without sitting down with book and a calculator and working through a power calculation, but I can tell you that, based on the relative incidence from one decade to another, it becomes easier the rarer it is.
Certainly in-- where you have an incidence of twenty per hundred thousand, in order to see a two-fold increase, which would be significant, you'd have to basically be looking at an incidence of forty per hundred thousand in a given population.

Q. But how many people would you have to study in an epidemiological study?
A. In order to do that responsibly, I would have to sit down with textbook and a calculator and work it out. I can't do it as we're sitting here.
Q. Do you know if any study has attempted to study the effects of benzene or benzene on 5q-?
A. Yes. Well, certainly in an occupational setting, benzene itself.
Q. Do you know of any studies that have looked for the incidence of 5q- or MDS among benzene-exposed workers?
A. When you're talking about 5q-, if you're talking about the chromosomal aberration, benzene workers were studied in that context.
Q. Those are the articles you cited earlier?
A. They're certainly referenced in the papers that I've provided. Golomb has looked at it. Several have.
Q. And these authors have found that there is a relationship, a causal relationship between benzene exposure and damage to the fifth chromosome, correct?

A. If you look at AML associated with
exposure to a source of benzene, as I said earlier,
you'd see an increased frequency of involvement of
chromosome 5. I don't think there is any doubt about
that. There are some who will argue that it has been
proven directly for benzene. I don't agree that that
is necessarily likely to prove to be any different,
especially since my own work demonstrates benzene is
capable of altering that chromosome along with many
others.
Q. You agree that benzene causes deletion
of the long arm of the fifth chromosome?
A. In the context of the evolution of AML,
yes.
Q. But weren't you using AML to look back
and then make your conclusion that there was a
benzene-induced event previously?
A. (No audible response.)
Q. Weren't you using the fact that a
worker might or a person might get AML to then
conclude that the chromosomal abnormality caused by
the fifth chromosome is related to benzene exposure?
A. The initial link is between benzene
exposure or exposure to chemotherapeutic agents and
the evolution of AML. Subsequent to that, it has

been demonstrated there is a very high frequency of involvement of specific chromosomes in AMLs that are associated with the evolution of that disease.
Q. Are these studies all involving people who have AML and then are looking backward at their progression?
A. Yes. The only opportunity we have to look at, at present, any progressive development of disease is where we have populations that are exposed to significant amounts of benzene. Right now the only one I'm aware of is in China.
Q. Which study is that?
A. I've referred to it in my CV. It is the NCI study of Chinese workers.
Q. Which one is that? Your CV is lengthy.
A. There is only one article on the subject. It's a study by Rothmiller. It's a huge study. It's basically epidemiologically based. There are a lot of potential problems with it. But it does certainly provide us with an opportunity to look at heavily exposed individuals. It's the only population that I'm aware of for which we have any characterization at all where we continue to have substantive exposures to

benzene.
Q. Did you bring that article there in your book?
A. No.
Q. That article is a prospective study?
A. It's a combination of retrospective and prospective. There are many articles that have come out on them. They vary in terms of what they find, in terms of what they report on. They vary with respect to quality. This is a very, very large study, and it's likely to be associated with production of dozens of papers.
Q. What is dose-dependent toxicity?
A. Virtually all effects, whether they're positive or adverse, that are associated with exposure to chemicals or drugs are characterized by what's called a dose-response. As you increase the dose, you increase the severity or the frequency of the response and, as you decrease the dose, you decrease the severity or the frequency of the response.
Dose-dependent toxicity simply means that the toxicity that's seen is-- follows a dose-dependent-- it can be characterized as a dose-dependent process. Virtually all processes,

including the potential for the development of cancer, are characterized by dose-response.
Q. So as you increase the concentration of exposure, you increase the severity of damage, you see bone marrow toxicity?
A. Yes. Basically going from no effect to severe bone marrow suppression. But you can look at it two different ways, and both are valid in this case. For a given individual, the probability that they will develop bone marrow suppression is dependent on the dose.
As I said before, not everybody that's exposed to even extremely high concentrations of benzene will show bone marrow suppression, but some individuals will. So the fractional response is subject to dose, just as the potential for an individual to develop symptomatology and the severity of that symptomatology can be associated with dose.
Q. That would vary from individual to individual?
A. To a certain extent, yes. Individual variability is a common feature of dose-response curves that involve populations.
Q. And the length of exposure, wouldn't that also increase the severity of bone marrow

toxicity?
A. Not necessarily. Depends on what your endpoint is. If an individual is susceptible, there's obviously some minimum duration of exposure that's going to be required to produce effects. For the same interval exposure or duration, you still see individuals that will develop toxicity and those that won't.
Q. That would be true at any level of exposure, wouldn't it?
A. No. At low levels of exposure, if you increase the duration, you don't necessarily-- if you're below a dose level and you have no demonstrable toxicity, increased duration of exposure is not necessarily going to produce any effect whatsoever.
Q. But no one can say that it will not produce such an effect, can they?
A. (No audible response.)
Q. They can say it, but is there any evidence to suggest that there is a known safe level of exposure to benzene at which bone marrow toxicity will not occur?
A. It is misleading, as I said before, to suggest that one can prove a negative. With respect

to the concentration of benzene, that is the point of departure between a level that no one will exhibit toxicity following exposure and some other concentration where toxicity can occur. There is no precise dose or duration product I can point to and tell you exactly where that is.
Now, having said that, there is plenty of evidence to indicate or to suggest that certain levels of exposure for periods of time ranging virtually to infinity are not associated with any adverse health effects associated with benzene. We're all exposed to benzene every day. And there's no evidence that will support the notion that exposure at those levels is associated with any health risk associated with bone marrow toxicity. So there's plenty of evidence to suggest or to indicate that certain exposure levels are not associated with health effects, and there is evidence to suggest that exposure levels at certain levels are associated with health effects in some individuals.
Q. Do you have an opinion as to whether there is a known safe level of exposure to benzene at which the various bone marrow toxicities which we've been discussing will not occur?
A. There are-- yes, I do.

Q. What's your opinion?
A. My opinion is that exposure to levels associated with ambient environmental levels.
Q. What is that?
A. Let's look at it from the standpoint of what science can-- what one can reasonably, reliably say with respect to the exposure to benzene that's associated with toxicity.
The scientific community-- within the scientific and medical community there is certainly consensus that chronic exposure to a hundred parts per million in air of benzene is associated with the potential to develop bone marrow toxicity, bone marrow suppression, cytopenia, aplastic anemia, and all of those individuals go on to eventually develop AML. I don't think there's anyone who would argue with that.
The evidence supporting a link between benzene exposure and bone mayor toxicity in any of those endpoints between fifty parts per million and a hundred parts per million is much less cogent, and the strength of that evidence is less.
Q. That is based on epidemiological studies?
A. Based on epidemiological studies, based

on anecdotal information with respect to occupational settings. That information is much less-- one can be much less confident in exposures at that level.
Q. When you say various endpoints-- I'm sorry. Go ahead.
A. I personally am concerned about exposures at that level. So I am an individual who thinks that bone marrow toxicity may be encountered in some individuals who are repeatedly exposed to the level of fifty parts per million. I am concerned about that. I can't say that that is a threshold. I'm concerned about exposures, chronic exposures between fifty and a hundred parts per million.
Q. Over what time period?
A. Over a period of time ranging certainly on the order of years, probably not months, but certainly on the order of years.
Q. So one year?
A. There are virtually--there are very few cases, even in the epidemiological literature, except where there's arbitrary inclusion of individuals who may have only worked for a very short period of time. The epidemiological literature probably can't support one year of exposure. Certainly exposures somewhere between-- on the order

of five years is certainly significant in the order of a hundred parts per million. And I wouldn't be surprised to see the same at fifty or to see the same at thirty.
When one starts talking about exposures, chronic exposures below fifty parts per million, the evidence both in the epidemiological or anecdotal literature becomes far less strong and less valid. There is a great deal of argument and controversy over whether exposures between twenty-five and fifty are associated with any adverse health effects in humans related to bone marrow suppression or the evolution of AML.
Below twenty-five, we don't have any data that is really extrapolable or based on risk assessment or other processes that don't involve direct measurement or analysis of exposure scenarios. There's no evidence that at one part per million there are any adverse health effects other than extrapolated again from mathematical models or risk assessments.
Q. There are risk assessments which indicate that there would be an increase in leukemia deaths at one part per million exposures, aren't there?

A. Risk assessments don't indicate effects, and they are not evidence of causation. They are simply mathematical projections tray are used for calculating probabilities that are useful in setting standards, but are not useful for-- they're based on policy, not science.
Q. But there are risk assessments which have been done based on epidemiological studies in the Pliofilm workers and others, and Infante's studies which indicate excess leukemia deaths at one part per million, aren't there?
A. No. They project on risk assessments that are made.
Q. They project that there would be?
A. If you look at the latest Rinsky study, which was published two weeks ago, which again is contrary to the majority of studies that characterize the same exposure, the same population with respect to exposure, the levels of exposure they find associated with bone marrow toxicity are on the order of thirty-four parts per million. And that is far below those that have been seen by others who evaluated that population, going back to Kipin studies.
The most recent long evaluation of risk

of leukemia in that population, Paxton, Poston--
there are several that suggest that the product
that's associated with the development of toxicity
and increased risk of leukemia is on the order of two
hundred parts per million.
Q. But there are other analyses which
indicate that there is an increased risk at one part
per million?
A. No.
Q. There are not?
A. There's no analysis based on exposure
data. There are mathematical projections. There's
no data base on which to opine that exposure to one
part per million will cause leukemia.
As a matter of fact, the OSHA standard
for exposure to benzene today is one part per
million. And, if you look at the criteria for the
establishment of that standard, that is an exposure
that an individual can be exposed to in a workplace
chronically, eight hours a day for forty years,
without evidence of adverse health effects. That is
a regulatory policy, and it's a standard.
Q. Have there been any studies of workers
that have been exposed to benzene in a workplace?
A. There are studies that include

populations that have had that type of exposure.
Epidemiologically, it's included in virtually any
epidemiological study. The petroleum workers, they
studied workers that have worked for forty years at
one part per million, including some of the exposures
within cohorts that have been studied in petroleum
refineries, workers that have been studied for forty
years at one part per million.
Evidence to support that one part per
million is associated with toxicity is virtually
non-existent. There are risk assessments that
project an increased risk above background for
individuals based on assumptions that are made using
the incidence of leukemia in populations that are
exposed to much higher concentrations.
The assumptions are many. They're
based on policy. They're not based on science. A
risk assessment is not-
Q. Which study-
A. A risk assessment is not evidence of
causation at any given concentration.
Q. Which epidemiological study has studied
workers for forty years at one part per million?
A. I don't-- as we sit here, I don't know
how many years the Wong and Raabe study has

captured. That study was forty-two years. That's the population of cohort that they captured.
Q. Which study?
A. The Wong and Raabe study from '95.
Q. What's the name of the study?
A. (No audible response.)
Q. Is that on your list? You can just tell me which tab it is.
A. Number 7.
Q. Is that a data analysis?
A. Yes. By definition it has to be.
Q. Did all the workers studied work forty years in the same industry?
A. No. They capture individuals that worked in the industry over that period. Some individuals will. Some individuals won't.
Q. How many people worked forty years?
A. Excuse me. It's a fifty-three year observation period. Okay. This is a retrospective study that looks at fifty-three years of follow-up in the petroleum industry and characterizes and calculates tie incidence of leukemia related to periods of exposure in ppm years.
I'm not sure, as we sit here, that I can tell you precisely what portion of the cohort

worked for what particular period of time.
Q. These were mortality studies, weren't they?
A. Yes.
Q. And they're looking at leukemia as an endpoint?
A. Yes.
Q. They're not looking for myelodysplastic syndrome or other blood dyscrasias, are they?
A. No.
Q. Wouldn't you agree with using leukemia as an endpoint in estimating the total risk of benzene exposure?
A. To the extent that myelodysplastic syndrome precedes the evolution of leukemia in some majority of individuals, that could be the case, except the transformation rate to AML and secondary myelodysplasia is on the order of eighty percent or greater. So the chance that, in fact, this particular type of study is going to include individuals that have persistent dysplastic phenomena, including leukemia, is relatively small because of the rate of transformation.
I do agree that, if one wishes to characterize at any given point in time the incidence

of disease associated with chronic exposure to high levels of benzene, that myelodysplastic syndrome should be included within that rubric. But, from a transformational standpoint, mortality studies capture that population in large part, because the transformation rate is so high.
Q. And if those studies showed an increase in the incidence of leukemia, wouldn't that also show an increase in the incidence of MDS?
A. That associates MDS preceding the evolution of leukemia, not MDS independent of leukemia, because, as I said, secondary myelodysplastic syndrome, which is a distinct disease from Sq- syndrome, is associated with a very high rate of transformation to AML and very high mortality in and of itself. The transformation usually occurs within a matter of months.
Q. Between MDS-
A. And AML.
Q. What literature supports that?
A. The chemotherapeutic literature looking at secondary myelodysplastic syndrome. The transformation rate is very quick.
Q. How about the benzene studies?
A. The benzene studies are retrospective.

They do not establish quantitatively a link between myelodysplastic syndrome and AML. If you look at the benzene literature itself, you can't draw tat conclusion, because myelodysplastic syndrome has not been included in the studies.
Q. You're drawing the conclusion from the chemotherapy studies?
A. I'm drawing some conclusion from that. There's an analysis of myelodysplastic syndrome, it's been seen in Chinese workers, again fairly high transformation rate. So some studies are beginning to confirm what we already know from the chemotherapeutic literature.
Q. What is the study that just came from China?
A. Some of it.
Q. Is it the Yin study?
A. Some of it. Yin is the first author. There are other authors as well.
Q. Does secondary myelodysplastic syndrome-- secondary meaning caused by benzene- proceed to AML or leukemia?
A. I would be surprised if a very large majority did not, probably on the order of eighty percent at least. Whether every one does is, I

think, not a question that I can answer at this time.
Q. Other than the Chinese study which you've cited-- and let me get the tab number on that if we could. Was that in your CV?
A. What?
Q. You were referring to a Chinese study?
A. The Chinese study I haven't provided, because I didn't think they were relevant to this particular issue.
Q. Not here. Okay. But you're suggesting that study is showing that?
A. Myelodysplastic syndrome has been seen in that study along with leukemia.
Q. That study indicated an increase of myelodysplastic syndrome?
A. That's what I mean by seen.
Q. Related to benzene exposure?
A. Related to benzene exposure.
Q. Does that study indicate what the exposure levels are?
A. Within the limits of occupational-retrospective occupational modeling, yes, it does, to a certain extent. It certainly indicates we're talking about high-level exposure.

Q. On the order of fifty parts per million?
A. My reading of it would be, at least cumulative exposure-- I don't know where myelodysplastic syndrome falls out in there in the rubric in their exposure characterization-- I would not expect to see them have any different pattern than what's seen with AML.
The problem you have in the Chinese study is you have twenty-five thousand workers significantly exposed to benzene. I don't know how many thousand sites. Characterizing the exposures is probably problematic.
However, based on individuals that we know have been exposed to high levels in China that are being followed and that have shown already significant signs of bone marrow poisoning, we ought to be able to get a better handle on the nature of the duration and levels of exposure that are associated with it.
Q. That hasn't been quantified yet?
A. There are-- they've quantizated cumulative exposure for the entire population. I don't think it's a particularly useful-
z Q. Do you know how large the population

that was studied?
A. They have at least twenty-five thousand captured in their exposure group. And I believe the initial study started out with over five hundred eighteen thousand workers. It's huge, and huge does not necessarily mean good. But it is a very large population.
Q. If you could just tell me again the title of that particular study. I believe it's in your CV.
A. Now, that one is just one paper in that whole series. That's not one that deals with the specific incidence of MDS.
Q. The one that you cited in your CV?
A. That one deals-- primarily looking at- that particular paper looks at parameters in benzene poisoned workers who have not developed leukemia.
Q. Which paper is that that we're talking about?
A. Rothman, et al. These are individuals that are exposed to high levels. They already have some demonstrable sign of benzene poisoning and toxicity.
Q. What year is that article?
A. It's in press.

Q. This one is?
A. Yes.
Q. How many of these articles that are listed in press did you bring as part of what you brought here today?
A. Those that are listed on the list of references that I provided are here.
Q. Can I get a copy of the Rothman article?
A. I should think so.
Q. It's not out yet I take it?
A. No.
Q. I'd like to, if I could get a copy of all the articles you've authored in press that were not included in the book.
A. I could do that.
Q. Okay. Other than the Wong study, were there any other epidemiological studies which indicate-- or the Wong study didn't indicate-- but are there any studies that studied workers working for forty years continuously at one part per million?
A. Probably not.
Q. Do you know what length of time the workers stay in their jobs, in the same job?
A. I think it varies with the industry and

it varies with time. That's one of the problems with capturing occupational populations is how long they stay in the job and where they-- whether or not they're captured in any given cohort.
Q. Are you aware of any studies today, as we sit here?
A. No.
Q. Do you know what the action level is for OSHA?
A. In OSHA, the permissible exposure level is one. The action level is, I believe-- I think it's .5.
Q. What is the significance of the action level?
A. That, in fact, you take steps to reduce the exposure level if, in fact, it reaches that point. It's an effort to prevent approaching the standard.
Q. Do you know what is required if the level reaches .5 parts per million by OSHA?
A. Specifically what's associated with the actions that are taken at that point in time, no, not as we sit here.
Q. How much benzene would an individual absorb working an eight-hour day at one part per

million?
A. Three million micrograms.
Q. Three million micrograms?
A. Yes. I actually calculated-- I actually used that in one of my calculations. On the order of three million micrograms per day or one part per million. I'm sorry. Did you say one or a hundred?
Q. One.
A. One would be on the order of thirty thousand.
Q. That would actually be absorbed?
A. If one assumes complete absorption, which is an overestimation, but for the sake of argument you can assume, I think, it's reasonable for comparison purposes, thirty thousand micrograms per day. And it's probably overly conservative in the sense that that assumes inhalation of about ten cubic meters of air in an eight-hour day, and that's probably high.
Q. Ten cubic meters is probably high?
A. Yes.
Q. What rate of absorption a=a you assuming, a hundred percent of what's breathed?
A. For the sake of simplicity, yes.

Q. Do you know what studies have been done to study what amount of benzene has been absorbed by inhalation?
A. If one looks at animal studies, one can obtain a fairly good estimate. At that level, you're probably talking on the order of somewhere between eighty and a hundred percent.
Q. Do you know of any human studies that have been done?
A. No. For the simple reason that it's not ethical to expose individuals to levels of benzene in particular, although I think that exposures at the OSHA level are certainly possible and practicable, and that individuals are exposed to levels that are similar to that or at least measurable in other situations.
Q. What is your concept of bioavailability?
A. Bioavailability is a major tenet of pharmaceutical development, and that is the amount of a chemical or a drug that is actually available for absorption into the body following introduction, whether it's in the gut, on the skin, through inhalation. Bioavailability is the amount of the material that is actually taken in by the body, and

it is usually some fraction of the total to which an individual is exposed.
Q. How is that measured?
A. There are a number of ways of going about measuring it. The most-- I think the most realistic and accurate approach is to look at the nature of the product and to measure how much of it is available. And there are a couple of ways of doing it.
From a worst case point of view, the best way to look at and most likely way, most accurate way to look at bioavailability is to characterize the release of a substance in the physiologic solution based under conditions that are likely to be found where the product is, whether it's the mouth, the stomach, the lungs, the gut, what have you, under conditions that mirror the Ph, time duration of transient physiological conditions. One can use animal data, but that's basically an extra population.
Q. Are there any models, established models, that have been established in the scientific community for such a physiological approach?
A. The pharmaceutical industry looks at bioavailability all the time. It is a frequent

component, if not a necessary component, in the submission of pharmaceutical preparations for registration of drugs with the-- certainly with the US FDA and ostensibly world-wide.
Q. How do they do that?
A. There may be animal studies. There usually are animal studies. There are also studies that look at individual formulations in the variations in either extractability or variability of various preparations.
Q. My question was: Are there any established models whereby a physiological model is created to test bioavailability?
A. Bioavailability is usually unique to a given preparation or formulation. Because of that, individual character, individual parameters that are used to determine what, in fact, is an appropriate model of bioavailability are case specific. That's similar to many aspects of pharmaceutics and drug development. The individual experiments, the individual results are specific to the agent in question and formulation in question. They aren't applied across the board to everything, but in fact are evaluated on a case specific basis.
Q. So there's no accepted model

established in the scientific-
A. There are models that are used all the time. To say that there is a single accepted model is, I think, misleading, because there is no model that is going to be appropriate for every given situation or every given formulation.
Q. Now, earlier you said that-- I believe you said that would be a worst case way to test bioavailability. Is that what you said?
A. Yes, I believe so.
Q. What would a better way to test it?
A. Well, one way to look at bioavailability which is done in some cases is in the process of evaluating and range finding for doses in humans is one way to look at bioavailality.
Q. By measuring the dose absorbed by a human?
A. Yes.
Q. Have you ever done a bioavailability study?
A. Personally, in the context of support for drug registration, no. In the context o= providing experimental parameters for experimental design, I've done studies that are comparable to bioavailab_1ity in the past. I haven't done any

recently.
Q. Have you ever administered-- been involved in any tests administering drugs or chemicals to individuals to test bioavailability?
A. No.
Q. Are you aware of any ethical standards which would apply to administering drugs or chemicals to humans?
A. That sounds to me like an oxymoron. I'm sorry, but standards aren't ethics. Standards are basically regulatory policies. Ethics, I mean if you're going to talk about-
Q. I said ethical standards.
A. Well, there are clearly questions related to the ethics of administering certain types of substances to people. That is an ongoing controversy in medicine and science today.
Q. Are there ethical considerations which you are aware of which would apply to situations where one wanted to administer drugs or chemicals to humans?
A. There are certainly procedures and paradigms that are predicated on ethics that are used in evaluating and administering drugs to humans, also chemicals. There are controversies related to the

administration of chemicals to humans that have no known benefit. That is a continuing issue in the toxicology field and probably will persist for many years to come.
Q. Is that also related to the potential harm from the chemical or drug administered?
A. If it's an ethical issue, it is not necessarily related to harm at all. I think that certainly, if we're dealing with a substance like benzene, the ethical question of can you intentionally administer benzene to an individual is totally separate and distinct from whether or not it would have any adverse health effect.
There's no evidence, as I said before, that exposure to individuals at the level of the OSHA standards have any adverse health effect. One could design a study to look at absorption and pharmacokinetics of benzene following administration of the equivalent of eight-hour, one ppm time-weighted dose without any expectation of producing adverse health effects. However, there, in fact, very well could be and there would be individuals who would say that that was unethical.
Q. Would you be one of those individuals?
A. No. But I--

Q. You don't think it's unethical to administer benzene to humans?
A. I don'-_ think that it would be strictly unethical to administer benzene to an individual in the context of an informed experimental study that could provide information that related to its distribution or metabolism in doses that are not associated with adverse health effects. By the same token-
Q. You said "informed." Do you mean-
A. Excuse me. I haven't finished my answer. By the same token, I recognize the ethical question, and I recognize that there are opinions that differ with that. There are also individuals who would agree with me. It is a controversy.
Q. Is benzene a carcinogen?
A. Yes, obviously.
Q. Would it be ethical to administer a carcinogen to individuals if they were uninformed?
A. The issue of ethics and the issue of- the issue, as I have been trying to say, that is a very controversial area or arena. There are individuals who would agree with me that the intentional administration of a substance for purposes of gaining valuable information with respect to

science is not unethical if it's done in an informed context.
What you have to keep in mind, this is an issue related to the ethics dealing with the intentional administration. The fact is we're all exposed to benzene every day.
If you drink water that is certified by the Environmental Protection Agency as clean, meeting the environmental standard, you are taking in approximately ten micrograms a day of benzene. If you eat, you're going to be exposed to benzene in eggs, dairy products, in meats. Anything that involves combustion is going to have some benzene in it. So you're ingesting benzene every single day.
One can quantitate the amounts. A purveyor of meats or dairy products I don't think is committing an unethical act by providing you with those products to eat, even though they have benzene. So, when you get into questions of ethics, I think you have to deal with issues that relate to dose as well.
The intentional administration of benzene de novo by itself is an issue that is currently controversial with respect to the ethics.
I'll give you a very good example. One could monitor

the absorption and distribution of benzene following administration of a dose of benzene that would be less than the amount that a smoker gets in a given day.
It's ethical to have a smoker smoke and measure benzene absorption or distribution. It is unethical or some people would consider it unethical to give that person the same dose of benzene by itself or a lesser dose of benzene by itself.
Q. Do the ethics turn on the-- you indicated that-- would it be ethical to administer benzene to someone for no known scientific purpose or with no perceived benefit to the advancement of medicine or science?
A. By itself, no. As a product of-- as a function-- I mean the intentional administration of benzene by itself, no. But the administration of benzene in the context of its presence in foodstuffs or drug products, I don't think there's-- that's an issue.
The fact is benzene is present in a great many different things. We're exposed to it every day. There's no such thing as zero. There's no such thing as no benzene. The question is how much is there, and whether it comports with or is

consistent with a dose of benzene that is not encountered in everyday life or that's associated with levels that are-- could produce adverse health effects.
The issue we've been talking about with the intentional administration of benzene is an issue now, because there are many very-- there are many individuals right now in the scientific and medical communities that are proposing precisely that, the intentional administration of benzene at doses sufficient to allow us to do reliable measurement of its distribution, metabolism in humans. Some of those individuals are exceedingly well regarded in the scientific and medical communities.
Q. Who are they?
A. Bernie Goldstein at Rutgers is one who is an advocate.
Q. What levels of benzene is he advocating administering?
A. Probably on the order of the OSHA standards.
Q. One part per million?
A. Yes.
Q. Would he administer this to unknowing individuals or would he inform them?

A. Those studies would obviously be scientifically designed experiments.
Q. Would it be unethical to do the experiment without informing the recipients of benzene that they're receiving a carcinogen?
A. For those experiments, no. But those are designed experiments with the express intention of administering benzene and only benzene for the purpose of the study. That's totally separate than the dairy farmer who produces milk that may contain trace amounts of benzene.
Q. How much benzene is in milk?
A. I'm not precisely sure. I'm more-- I'm more confident about the amount that's present in eggs. Eggs have a fairly high concentration of benzene.
Q. What is the content of eggs?
A. I think I calculated it once. I think that, depending upon who you believe in terms of the analytical measurements, that a boiled egg contains somewhere between ten and fifty micrograms of benzene. But, again, T wouldn't swear to those numbers. I think the range is probably safe. The EPA has measured the average intake of benzene for an individual who is not a smoker or

not exposed to smoking in an occupational setting, and it varies. Various studies I've seen suggest the range of background levels of benzene intake is a hundred and fifty to eight hundred micrograms a day for everyone of us. If you're a smoker, you can multiply that by about three or four.
Q. It's not possible to produce eggs without benzene, is it?
A. I don't know. It's possible to produce eggs without cholesterol.
MR. WHITNEY: I'm not going to qualify the doctor as a poultry expert, so-
MR. WILLIAMS: Do I have your promise on that?
Q. (BY MR. WILLIAMS) Could you conceivably do a bioavailability study of benzene available from Orafix Special by placing Orafix Special in people's mouths and then attempting to measure the benzene, labeling the benzene, and then measuring the effect on the person?
A. I think that the design of that experiment would be cumbersome and probably less accurate than determining the worst case scenario. That is the amount of benzene that's released in a physiological solution under the conditions that

we're likely to find in the mouth or elsewhere.
Q. Could you do it though?
A. Pardon?
Q. Could it be done?
A. I think it would be less reliable than the worst case methodology.
Q. That's not my question.
A. Could you do it, could you do a bad experiment? Yes.
Q. You could do that experiment?
A. You could do that experiment. It would not be a good experiment.
Q. Would it be ethical to do that experiment, not tell them you were giving them a carcinogen?
MR. WHITNEY: Objection.
A. If you were doing an experiment for the purpose of measuring benzene, under current standards of ethics in human use or experimentation, one would be required to tell them what you were doing, why you were doing it, and what you were going to measure. Therefore, you could not intentionally give them anything, even if in fact it was candy, if you do not tell them what the purpose is and what it is you're trying to measure.

Q. (BY MR. WILLIAMS) I digressed a little bit, but I asked you questions about levels. I don't believe I ever got an answer to the question of do you have an opinion that there is a known safe level of exposure to benzene at which bone marrow toxicity will not occur.
MR. WHITNEY: Objection. I think the question has been asked and answered.
MR. WILLIAMS: It wasn't answered.
A. I believe there is no evidence that would support a causal relationship between chronic exposure to benzene at one part per million and any adverse health effects in humans. I think that there's no evidence that exposure to ten parts per million, which is above current regulatory standards even in an occupational setting, would produce ill effects.
There is controversy associated with that exposure between twenty-five and thirty parts per million, although there's no reliable data. I already discussed what the level of evidence is associated with exposures of fifty parts per million to a hundred parts per million. Somewhere between fifty parts per million and a hundred parts per million ambient exposure there's a probably a level

of benzene that produces a demonstrable effect.
Whether that's associated with any adverse health
effects, we have no information that would allow us
to reach an opinion.
I think at the OSHA standard and at
concentrations less than the OSHA standard there's no
reliable or demonstrable evidence of adverse health
effects associated with exposure at that level.
Q. (BY MR. WILLIAMS) Is it your opinion
that there is a safe level below which bone marrow
toxicity will not occur?
A. I am saying that there's no evidence to
suggest that that level of exposure is associated
with any adverse health effects.
Q. But are you saying that there is a safe
level below which-
A. If your definition-
Q. =- no known bone marrow toxicity will
occur? Let me finish my question.
A. If your definition of "safe" is that
there are no adverse health effects, then we can use
the word "safe". What I am saying is that there are
no adverse health effects that have been demonstrated
associated with benzene exposure at that level.
Q. But what I'm asking you for is your

opinion as to whether or not there is a known safe level of exposure to benzene at which bone marrow toxicity will not occur, and, if there is, I want your opinion as to what that safe level is, below which bone marrow toxicity will not occur.
A. I think I've answered that, but I will say it once more. Certainly, at the level of one part per million, there is no evidence that repeated exposure, chronic exposure to one part per million in air will produce any adverse health effects, including bone marrow toxicity.
I do not believe that one ppm is the demarcation between an exposure to benzene that would produce toxicity and one that won't. One ppm I believe does not result in any adverse health effects including bone marrow toxicity. The precise point at which chronic exposure can lead to the evolution of bone marrow toxicity, I do not know precisely what that concentration is.
Q. Is it fair to say you also do not know at what precise point the exposure to benzene will not lead to bone marrow toxicity?
A. As I've said before, science cannot prove a negative. I can't answer that question.
Q. Would you be speculating to give a

point at which-- below which bone marrow toxicity will not occur in response to benzene exposure?
A. With respect to a given concentration, it is not speculation for me to say that there is no scientific or medical evidence that will support that it does occur. That I can do. What I cannot tell you is what concentration of benzene is associated with, what concentration is not associated with. There are no studies that can prove a negative. There are no studies to support that exposure to one part per million will produce those effects, and certainly not at lower levels.
Q. But you are unable to say that there is a point below which bone marrow toxicity, MDS, the various blood dyscrasias that we've been talking about so far today will not occur; isn't that true?
MR. WHITNEY: Objection. This line of interrogation is becoming harassment. He said you can't prove a negative.
Q. (BY MR. WILLIAMS) So you can't give me a point below which it would not occur?
A. I can tell you at a given concentration whether there is any evidence to suggest that it can occur. And I'm telling you for purposes of discussion that the current OSHA standard of one part

per million is a concentration of exposure that has not been demons-rated to be associated with any adverse health effects.
Q. And what studies show that; you're basing it on what studies exactly?
A. Based upon the sum total literature associated with benzene toxicity. There's no-
MR. WHITNEY: Don't cut the doctor off. He's been very patient all day now.
A. There's no evidence to support the contention that exposure at the current OSHA standard produces bone marrow toxicity.
Q. (BY MR. WILLIAMS) There's no such evidence?
A. There's no such evidence that indicates exposure at that level is associated with adverse health effects. The evidence in the clinical literature does not support that.
Q. You're not aware of any cases in any of the studies where individuals were exposed to approximately one part per million and developed leukemia?
A. The design of retrospective studies involves the selection of cohorts that are exposed to a substance, and hopefully, under a control or not,

in any retrospective study you expect to see cases of disease that appear spontaneously at the same rate as they would in the general population.
It is, therefore, misleading to suggest that in any given population you won't have spontaneous disease occurring. I cannot tell you that there has not been a case of leukemia or myelodysplasia that has occurred in individuals exposed to benzene at one part per million or less. What I can tell you is it is much more probable than not that, if they did, it is a spontaneous lesion and not one associated with benzene.
Q. Have you ever testified before that there is a level of exposure to benzene which you would consider to be safe?
A. I have testified that I believe benzene toxicity follows a threshold. I have discussed the evidence many times with respect to the nature and strength of the evidence associated with a given exposure scenario, much as I have today.
Q. But I'm asking you, have you ever testified before that there is a level of exposure to benzene that you consider to be safe? That's a very simple question.
A. I believe i have, and I believe I said

it today. We have been talking repeatedly about one part per million. And I don't think exposure to less than one part per million is of any consequence.
Q. So it's your opinion that exposure to one part per million is safe, and that below that one cannot get any bone marrow toxicity?
A. It's my opinion that exposure to one part per million will not produce bone marrow toxicity, and certainly exposure less than that is not associated with bone marrow toxicity.
Q. Is it your opinion that that is safe?
MR. WHITNEY: Objection.
Q. (BY MR. WILLIAMS) At that level?
MR. WHITNEY: He just answered it.
A. I believe I've answered that.
MR. WILLIAMS: Read the question and answer back, please.
(Whereupon, the reporter read the question on page 149, line 4, and the answer on page 149, line 7.)
Q. (BY MR. WILLIAMS) Would you consider one part per million to be a safe level of benzene exposure?
MR. WHITNEY: Objection. He answered the question.

Q. (BY MR. WILLIAMS) Do you consider-- is it your testimony-- I just want to make sure we have it all straight here-- that exposure to benzene levels of one part per million is safe, and below that level there would be no chance of having bone marrow toxicity?
MR. WHITNEY: Objection again. You can answer one last time, and after that I'm going to instruct you not to answer, because that is harassment.
MR. WILLIAMS: Well, as long as we get an answer to the question.
A. I believe that, based upon all the evidence that we've discussed today that I've referred to with respect to what we know about benzene toxicity, bone marrow toxicity, that the chances of developing a particular manifestation of bone marrow toxicity in an individual exposed to one part per million is the same chance of an individual who is exposed to any concentration of benzene or no benzene. It's the same. There's no evidence to suggest that that level of exposure is associated with bone marrow toxicity.
Q. (BY MR. WILLIAMS) Do you consider that to be a sate level of exposure as a toxicologist?

A. If you define "safe" as meaning that there are no adverse health effects associated with that exposure, then I can accept your definition of "safe".
Q. I thought your definition of "safe" is a level below which no bone marrow toxicity will occur?
A. Well, I've said that probably ten times this afternoon.
Q. As a toxicologist, can you state that the level of one part per million ambient exposure is a level below which there would be no bone marrow toxicity?
A. I'm saying that there is no evidence that that level of exposure could produce bone marrow toxicity.
Q. Can you or can you not, as a toxicologist, say that there is a safe level below which bone marrow toxicity couldn't be produced? It's a yes or no question.
A. The nature of scientific inquiry and evidence requires that one, in fact, use data and evidence to support an opinion. I am saying there is no evidence that I can point to that will allow me to say that exposures at that level are associated with

any adverse health effect.
Q. But, as a toxicologist, can you pinpoint a point below which there would be no adverse health effects, no risk of-
A. I cannot.
Q. I'm not asking you for a recap of epidemiological studies. I'm asking you, as a toxicologist, about benzene, what you know about benzene, and how it's metabolized, and how it affects bone marrow; can you state that there is a point below which adverse bone marrow effects cannot occur?
A. You're asking me to essentially if I can prove a negative, and I cannot do that.
Q. Can you do that-
A. As a scientist I cannot.
Q. -- as a toxicologist?
A. As a scientist, I cannot absolutely say that something will not happen. There's a finite chance that anything can happen. I'm saying there's no evidence to suggest that benzene at those concentrations will produce that type of an effect.
Q. You're basing it on the studies you brought today?
A. And the literature associated with

benzene in general.
Q. As a scientist, as a toxicologist, you cannot say that below a certain point there would be no effects?
MR. WHTTNEY: Objection. He's answered the question.
Q. (BY MR. WILLIAMS) Is that correct?
A. I've already stated what the restrictions are placed upon me as a scientist in rendering an opinion.
Q. Right. With those restrictions in mind, as a scientist, as a toxicologist, you can't say that there's a point below which-- there's a point of benzene exposure below which there would be no adverse bone marrow effects?
MR. WHITNEY: Objection. He's answered the question. Why are you pursuing this? He's answered the question. He has answered the question. You don't like his answer. He's answered it.
MR. WILLIAMS: Calm down, Dan. Go ahead, Doctor.
A. I believe I've answered the question.
Q. (BY MR. WILLIAMS) Is the answer no, you can't?

A. I've stated I cannot prove a negative.
Q. So you can't state a point below which there would be no adverse effects as a scientist?
A. As a scientist, I cannot tell you absolutely that the sun will nor- rise in the west tomorrow. But also, as a scientist, I can tell you that every piece of information I know or have a: my disposal would lead me to conclude that the probability of that happening is virtually nil. I have essentially said the same thing with respect to benzene exposure at the level of one part per million.
Q. Are there any studies which establish a minimum amount of benzene necessary to cause adverse bone marrow effects?
A. Are you talking about a cumulative dose? Are you talking about an absolute amount? Are you talking about a concentration?
Q. Any of the three.
A. Well, they're different. We've already discussed the issues, the evidence related to chronic exposure to a concentration of benzene in air of a hundred parts per million, fifty parts per million, what have you, if that's your definition. And the answer is yes, there is

evidence to suggest that chronic exposure to benzene at a hundred pa=is per million is toxic to bone marrow.
Q. Is that a minimum? Are there studies that have established a minimum level of benzene-
A. We've been through that.
Q. -- necessary to cause-
A. And we've been through that. That's the same discussion. I've related to you what the evidence is associated with exposures to a hundred parts per million or greater. The evidence is less reliable between fifty and a hundred-
Q. Okay.
A. -- so on and so forth.
Q. Are there any studies that establish a minimum level of benzene necessary to-- minimum amount of benzene ingested orally necessary to cause a bone marrow toxicity?
A. One can relate-- one can relate absolute amounts between-- of a substance between inhalation and oral. For example, we've basically done that when we discussed exposure at the one ppm standard in air by OSHA. It represents about thirty thousand micrograms per day, which would be the same dose that you would receive if you ingested the

thirty thousand micrograms per day. One can do it at a hundred parts per million. One can do it at fifty parts per million.
The problem that you get into, depending upon what question you're asking, is that the product of cumulative exposure is not necessarily related to toxicity. It may roughly mirror it. But, if there is a threshold, a concentration below which no toxicity is seen, cumulative exposure can be misleading.
Let me give you an example. The epidemiological studies, for reasons that are based on limitations in what they can measure, tend to relate everything to cumulative exposure. Dr. Wong's study talks about risk of leukemia below and above two hundred ppm years.
Two hundred ppm years is a product. It could represent exposure to one ppm for two hundred years or exposure to two hundred ppm for one year. Those are basically totally different scenarios.
I personally would have no concern about exposure to one ppm for two hundred years. Obviously, two hundred years is ridiculous. But for that I would expect absolutely no relationship with leukemia. On the other hand, exposure to two hundred

ppm for one year could be significant.
Now, for both of those we can calculate
an absolute dose. That is why, when I have evaluated
the potential exposure scenarios in this case, I have
basically expressed them in amounts per day as
opposed to some total number.
MR. WILLIAMS: Let's take a break.
(Whereupon, at 2:42 p.m., a recess was
taken.)
Q. (BY MR. WILLIAMS) Doctor, when were you
first contacted in this case?
A. Mid-July, I believe.
Q. Who were you contacted by?
A. Mr. Whitney.
Q. And what were you told at that time?
A. I was asked if I would evaluate the
medical records and information available on the
product Orafix, and arrive at a conclusion as to the
potential relationship between exposure to benzene
and the development of Ms. Lakie's disease.
Q. This was in July of '95?
A. Yes.
Q. Do you have a-- subsequently enter into
a retainer agreement with Mr. Whitney's firm?
A. I arrived at an agreement with respect

to serving as a consultant and expert. I wouldn't characterize it as a retainer.
Q. Okay. When was that agreement entered into?
A. At approximately the same time. I believe he contacted me by phone first, and then sent me the material and a letter outlining the issues in the case.
Q. Did you-- is this agreement in writing?
A. Our agreement?
Q. Yeah.
A. No.
Q. Can I see your file?
A. (Complying.)
Q. Did you keep time records on your time spent in this case?
A. Yes, partially. I have included there a record from September through preparation for a deposition today. I have a previous invoice that I submitted and was paid that I cannot find a copy of. As I sit here, I recall that that was on the order of seven thousand dollars.
MR. WILLIAMS: Let's mark this Exhibit 4.
(Whereupon, a document was marked Irons

Deposition Exhibit 4 for identification by the reporter.)
Q. (BY MR. WILLIAMS) Was the first invoice through the first date on this time sheet which is marked Exhibit 4?
A. It was up to that. I believe it ended in September.
Q. Okay. So it's for the initial hours you spent?
A. Yes.
Q. And would that include the days and hours each day you spent reviewing the materials?
A. Yes.
Q. (BY MR. WILLIAMS) Do you have a copy of that invoice, Dan?
MR. WHITNEY: Probably.
MR. WILLIAMS: Can I get a copy of that?
MR. WHITNEY: (Indicating.)
Q. (BY MR. WILLIAMS) And what is-- is this second invoice through April 8 complete?
MR. WHITNEY: That's not an invoice.
A. That's not an invoice.
Q. (BY MR. WILLIAMS) I'm sorry. Time sheet.

A. It doesn't include preparation. It doesn't include today or yesterday in preparation for this deposition, but up until then it's accurate.
Q. It's accurate through the 8th?
A. Yes.
Q. And, between the 8th and yesterday, did you spend any time on this?
A. I don't believe so. If so, it was on the order of a half hour or so prior to yesterday.
Q. And what did you do yesterday in preparation for today's deposition?
A. Mr. Whitney-- I met with Mr. Whitney to go over the essence of my opinion as it related to this case, and to go over the documents that I would be producing today.
Q. When did you meet with Mr. Whitney?
A. Yesterday afternoon.
Q. What time was that?
A. I think it was one o'clock or a little after.
Q. Did you meet at your office?
A. Yes.
Q. How long did you meet for?
A. Till approximately 5:00 or 5:30.
Q. And you essentially went over the

opinion which is part of Exhibit 3; is that a fair statement?
A. Yes.
Q. Do you have any new opinions to add to what you already stated in your initial opinion prepared in September?
A. I went over further calculations I'd done with respect to various exposure scenarios which are not present in my report because I didn't have the information.
Q. Is that reflected on this yellow sheet with calculations in Exhibit 4?
A. Yes.
Q. Why don't you tell me what those are?
A. I went through a variety of estimates for potential exposure to benzene associated with Ms. Lakie's use of Orafix, a range of different estimates based on widely different assumptions. In my initial report, I based my conclusions based solely on Dr. Jacobus's analysis.
I also performed a number of other calculations and compared those levels to levels that are associated with benzene toxicity.
Q. Can I see that?
A. (Complying.)

Q. What are your-- did you calculate the absorption at various levels of assn=lions, at different assumptions?
A. I'm not sure I understand the question. What I did-- first of all, I still think that Dr. Jacobus's analysis of bioavailability is the most likely, the most reasonable analysis. Nevertheless, I used a number of other assumptions to evaluate the potential exposure scenario. What I determined as a worst case scenario was I assumed a hundred percent bioavailability of benzene, which I think is not supportable, but for purposes of assumption and discussion I did that. I then determined, based upon what I have been told, the worst case scenario for the amount of benzene that is present in the original Gantrez. I assumed a high level-- I assumed a level of Gantrez in Orafix.
Assuming a hundred percent bioavailability, I used no corrections for absorption and calculated, based upon Ms. Lakie's testimony, the amount of material she used over a thirty-day period, translated that into grams, and calculated based upon assumption of the highest level of benzene in Gantrez, highest level of Gantrez in orafix, and no

corrections for bioavailability what the total amount of benzene would be, in other words assuming that every amount of benzene that could be associated with the product was absorbed.
And I used those numbers and compared those to values of exposure on a daily basis that are associated with the OSHA occupational standard or with adverse health effects. I then went through-
Q. Let me interrupt one second. Did you do a daily dosage?
A. Yes.
Q. Assuming a hundred percent absorption?
A. Right. Based upon worst case numbers, I obtained a range of exposure between nine thousand and ten thousand micrograms per day.
Q. What's the range based upon?
A. Based upon-- she gave two different numbers with respect to her use of a large tube or a small tube, which have different amounts in them. And if you use-- if you extrapolate those into days, you come up with slightly different use, like between two and 2.4 grams of Orafix. And I took those numbers and basically used those to estimate a range.
Q. And your range is nine thousand to ten

thousand eight hundred micrograms per day?
A. Micrograms per day, assuming total that the amount of benzene present was always at the level of the highest amount present in Gantrez, the Gantrez was present at fifteen percent all the time in Orafix, and that there is a hundred percent absorption.
Q. And what percentage of benzene did you assume was in the Gantrez?
A. .3 percent.
Q. What did that translate to in terms of the Orafix Special as in terms of parts per million?
A. Parts per million is a relative term. I mean parts per million in Gantrez is a relative term. I think it's more-- it makes more sense to talk about absolute amounts.
Q. Okay. What does .3 percent benzene in Gantrez translate to?
A. Well, three percent times fifteen percent times two to 2.4 grams gives you basically .009 to .011 grams per day of product, which is equal to nine to ten micrograms per day or nine thousand to ten thousand micrograms per day of benzene.
Q. So-- I'm sorry-- you're assuming three

percent or .3 percent, .3 percent benzene in the Gantrez, right?
A. You know, actually you're right. This number overestimates by an order of magnitude the amount that's really present, because I took the three-tenths of a percent. It should have been three percent, not three-tenths of a percent, so this number is actually divisible by ten. It's nine hundred to a thousand eighty, not nine thousand to ten thousand.
Q. Whichever figure you use, nine hundred to a thousand, nine thousand, ten thousand, or Jacobus's figures, does it change your opinions or your conclusions in the case?
A. No. No. Basically, even assuming the numbers I have that have a mathematical error in them, the level of exposure is less than the occupational standard of an individual exposed to one part per million.
Q. Is that pretty much the basis for your opinion in the case that exposure is insufficient to cause the disease?
A. It is one of my opinions. Causation is an issue that relates to, one, the plausibility that the disease is associated with the exposure at any

level, what the dose is, and what the likelihood is the disease is caused by that exposure.
In this particular case, I believe that 5q- syndrome is an independent and distinct entity, it's not associated with secondary myelodysplasia, and that the incidence of that disease in Mrs. Lakie's age group is high relative to the general population.
Q. What is the incidence in her age group?
A. It is between seventy and seventy-nine, it's approximately twenty per hundred thousand.
Q. Between seventy and seventy-nine?
A. Age group.
Q. 5q-?
A. Or the incidence of myelodysplastic syndrome in total is on the order of twenty per hundred thousand. The 5q- syndrome is associated with individuals roughly between the ages of the mid-forties through the eighties, with a higher incidence that is at least reflected in the literature of occurring in the fifth and sixth decades.
Q. Okay. So I don't want to lose these points as we go along. In the age group seventy to seventy-nine, the incidence of MDS is twenty -c a

hundred thousand?
A. Yes, a- least in one study.
Q. Do you have figures on what the incidence would be in the sixty to sixty-nine age group?
A. No, I don't. No, I don't. Certainly, if you reflect on the studies of 5q- syndrome, the typical patient is a female, age greater than fifty or around, within the fifth decade or later, that presents with a refractory anemia.
Q. Right. Just in terms of incidence, do you have any figures on the incidence of myelodysplastic syndrome, 5q-, in any of these age groups?
A. For age-- for age corrected or age independent, it's on the order of two to 2.9, I believe, 2.3.
Q. In total population?
A. Per-- yes, or-- it's either total population or males.
Q. Or males?
A. Or males
Q. Is that what you're talking about, MDS, 5q-?
A. No. For total MDS.

Q. Do you know of any figures for 5q-?
A. For a precise number, I do not know of a study that provides that information.
Q. Okay.
A. The point I was making was that Ms. Lakie falls into a category that is frequently reported as being associated with 5q- syndrome, that its prognosis and presentation is different than that that's associated with secondary myelodysplasia. Therefore, apriori her disease does not constitute and her presentation was not one that I would find to be what you'd expect to see following exposure to benzene. Had I evaluated the dose-response, the data with respect to the potential exposure to benzene, its end product, I also don't see that, in fact, the level of exposure would constitute that which is associated with the production of toxicity associated with benzene.
Q. That was my initial question. That was with respect to the OSHA standard, correct?
A. Yeah. The OSHA standard I used strictly as a matter of comparison. I also compared it with exposures we've discussed today in terms of where there's varying levels of evidence to indicate bone marrow toxicity, and I calculated those in terms

of the absolute amount that would be associated with that exposure. So those are, in fact, the comparisons that I made.
Q. That's what you used for that aspect of your opinion related to dose?
A. Yes.
Q. Okay. What medical records did you review, and when did you review them?
A. I reviewed-- well-
Q. Let's pull them out. Are they all there?
A. They're all there, and they're all over.
Q. You mean they're all mixed up?
A. Yeah.
Q. Do you recall which medical records you reviewed?
A. (No audible response.)
Q. Are these all medical records, or does this also include depositions?
A. It includes depositions. It includes everything that I received to my knowledge. I included medical records, and the reports that characterize basically these notes are obviously a very small reflection of the medical records, but

those reflect the points that I made at the time I read the records.
Q. Why don't you number these yellow pages which are part of Exhibit 4, and we car refer to them by page number if we need to?
A. (Complying.)
Q. So page 3, you just numbered the notes you made on medical records which you reviewed?
A. Yes.
Q. Did you review the records from Dr. Swerdlow and MCV?
A. Yes, I did.
Q. Did you review the records from the Mayo Clinic?
A. I'm not sure precisely what you're referring to.
Q. That would be-- you indicated that you did in your report on September 12?
A. I'm just not recollecting precisely which records came from which-
Q. Let me ask you this: Does that top paragraph on page 2 of your report, does this pretty much give a complete recitation of the records that you reviewed?
A. At the time of this report, yes.

Q. Okay. Had you reviewed medical records subsequent to the report?
A. Not medical records per se that I recall. I have reviewed additional reports and other material that I've received.
Q. Have you received any ocher medical records since the date of your report?
A. I don't specifically recall.
Q. Did you-
A. I could look through the stack here, but I also don't think that what I have here is going to tell me precisely when I received it.
Q. Okay. Do you agree with Ms. Lakie's treating physicians as to the diagnosis of her disease?
A. 5q- syndrome, refractory anemia with ringed sideroblasts. Based upon the descriptions I've seen, I see no reason to disagree with that diagnosis.
Q. The diagnosis is myelodysplastic syndrome, 5q-, and then with the other things you mentioned, a refractory anemia, ringed sideroblasts, leukopenia, hypercellular bone marrow?
A. At the risk of quibbling, I'd say that myelodysplastic syndrome is basically the broader

rubric under which refractory anemia is seeded. And that is why the diagnosis is there. It isn't myelodysplastic syndrome and refractory anemia.
Q. Okay. It's myelodysplastic syndrome, 5q-?
A. 5q- syndrome associated with a FAB classification of refractory anemia with sideroblasts in the context of myelodysplastic syndrome. I have no problems with that.
Q. It's under the rubric of myelodysplastic syndrome?
A. Yes.
Q. Her disease is under that rubric?
A. Yes, it is.
Q. The FAB classifications are not cytogenetic classifications, are they?
A. They're not even based upon the cytopenias per se. The strict FAB classification is based upon the bone marrow morphology.
Q. Okay. When did she-- in your review and in your opinion when did she first-- when did she come down with myelodysplastic syndrome?
A. Can I-
Q. Sure.
A. I believe there's one report by Dr.

Swerdlow that indicates that the macrocytic anemia was present as early as 1988. Somewhere I may have the precise date. But if, in fact, that's accurate- and I have no reason to believe it isn't-- that would, I think, be consistent with when it was first apparent.
Q. The myelodysplastic syndrome?
A. Yes, because that's part and parcel of the refractory anemia.
Q. Okay. Would the clonal aberration have been apparent at that point?
A. Most likely, yes. Most likely I say- I never say never in this field-- but most likely, yes.
Q. You expect the clone to be present?
A. Be present at the time of diagnosis, if there were sufficient numbers of cells present from the clone. But, of course, there again with diagnosis you expect there would be, because there would be a reason for performing the test in the first place, which is the symptomatology.
Q. Which does-
A. The cytogenetic, the bone marrow characterization.
Q. Do you know when that was performed?

A. I could find it relatively easily. I don't know precisely. Wait a minute. I believe it was in October.
Q. Which year?
A. '90.
Q. Okay.
A. My point is that you would most frequently find it associated with the manifestation of the anemia. When you expect to see it is when it's most frequently seen.
Q. In what type of cases?
A. In most cases in myelodysplastic syndrome, if you're going to find a clone aberration, it tends to be present at the time of diagnosis. It's the earliest finding with respect to a genetic finding when you see it.
Q. Now, part of the symptoms of Ms. Lakie's disease include bone marrow depression; is that correct?
A. Well, technically that's not a symptom. It's a sign. But bone marrow, yes. She has an anemia, which is consistent with bone marrow suppression, and she's got a cytopenia, predominantly of neutrophils, which is consistent with bone marrow suppression. And all of that is consistent with what

you usually see in secondary myelodysplastic syndrome.
Q. Why is that?
A. Because, as I said before, you usually see a thrombocytopenia or a lymphocytopenia, one or the other or both. Those are usually the cell lines that are predominantly involved.
In spontaneous cases of refractory anemia, one tends to see neutrophils predominantly involved. And that's a pattern you don't see following benzene usually.
Q. Is this based upon diagnostic studies?
A. Based upon characterization of patients that have appeared in the literature as well as what we know about patients following chemotherapy.
Q. These are based on review of literature that you've done?
A. Yes.
Q. You don't treat patients; is that correct?
A. I do not treat patients. I do consult in differential diagnoses of hematologic diseases based on characterization of diagnoses and laboratory findings.
Q. So you haven't treated patients with

5q-?
A. No, I have not.
Q. Which studies indicate that depression of the neutrophils is not something that would be associated with benzene exposure?
A. Again, you're asking me to prove a negative. What I can do is point to studies that show involvement of decrease in platelets and other lymphocytes, with a relative sparing of neutrophils. Some of the Aksoy studies demonstrate that. The Goldwater study is the first controlled study of exposed workers, and that study characterizes absolute lymphocytopenia as one of the first findings, and the relative sparing of neutrophils. You'll find references to that sporadically throughout the early literature on benzene. And it's also consistent with what's seen in the chemotherapy, where you don't have complete presence of the bone marrow to begin with. My point there being, if you give a dose of bone marrow that ablates the bone marrow, you don't have enough of anything present that you can point to. And that frequently is seen following inventive chemotherapy.
Q. Other than the study-- is the study you

mentioned just now Goldwater?
A. Goldwater.
Q. Are there any studies which indicate that?
A. I believe several clinical-- at least one clinical review by Bernie Goldstein confirms that.
Q. Is that included in your materials today?
A. No.
Q. Is the Goldwater?
A. Yes.
Q. Okay. Which tab is Goldwater under?
A. Three.
Q. And which Goldstein article were you referring to?
A. One of the reviews he's written in the last several years. I couldn't, as we sit here, tell you precisely. This is not-- this concept is not arcane. It's referred to often in the literature. And I think it's reasonably well accepted by most people in the field.
Q. Do you know what Ms. Lakie's leukocyte count is now?
A. As we sit here, no.

Q. Do you know what her platelet count is?
A. No. Certainly everything that we have reviewed in terms of her medical records suggests that it was normal, low normal.
Q. Wasn't her platelet count, in fact, low in August of '95?
. A. Her platelet count, I didn't see any numbers that were consistent with a problem with platelets as in a thrombocytopenia. Relative decreases in platelets relative to her initial presentation I do believe I saw.
But I didn't see any numbers that were outside-- that were basically below the range of normal function, which would be certainly below fifty thousand per cubic millimeter. Something in that range I didn't see.
Q. But they were below normal range for that test than one would expect to find?
A. Within a normal range, but not a presentation-- I would say her platelets were marginally normal. She certainly would not be characterized as having thrombocytopenia. And that is not the characterization that her treating physicians gave either.
Q. But they were lower than normal, they

were lower than the normal range?
A. They were not physiologically below a range of normal function. And I don't believe that the early measurements were necessarily below a normal range, depending upon what range you're going to call normal.
Q. You're referring to the range in August of '95?
A. Specifically in August '95 or when she presented are you talking about?
Q. When she presented. My. question was August '95.
A. I'd have to look at that. I'm not sure.
Q. You don't know, as we sit here today?
A. I don't. I don't think it's relevant to the issue.
Q. Why is that?
A. Because that's-
Q. When she was diagnosed with the disease?
A. She was diagnosed with the disease in basically '90.That's five years prior.
Q. Of what significance is that?
A. Actually I have noted here in October

of '90 her platelets were normal. That's my note based upon my review of that.
Q. Okay. Of what significance is that?
A. It's just not a pattern that I think is consistent with what you'd expect if-, in fact, at that point in time she was being exposed to benzene at levels that would produce bone marrow toxicity. I'd expect to see a lower platelet level, and the neutrophils to be actually spared.
In her case, she has lower neutrophils, relative sparing of lymphocytes, relative sparing of platelets.
Q. And low red blood?
A. Yes.
Q. And she did have leukopenia?
A. Marginally, yes. Her white count was thirty-six hundred. That's not leukopenic by most normal ranges. That's marginal. That's low normal.
Q. And--
A. She had a macrocytic anemia, a slightly lower hemoglobin.
Q. And you do see macrocytic anemia in conjunction with benzene cases, don't you?
A. It's one of the findings that has been seen, but it's only one.

Q. Ms. Lakie also has a functional abnormality in the growth of her blood precursor cells, doesn't she?
A. That comes with the disease.
Q. That's part of her disease?
A. Yes.
Q. Do you have an opinion that 5q--- that MDS, 5q- cannot be caused by benzene?
A. I do not believe that the 5q- syndrome is associated with exposure to benzene at any level. The production of a 5q- chromosomal aberration in the context of secondary myelodysplasia or the development of AML, I've already testified to, I do believe that that can be associated with benzene exposure.
Q. What is it about 5q- which makes you say that it is not associated with benzene exposure?
A. 5q- syndrome clearly presents a different constellation, different events. There may be ringed sideroblasts. It does not have the same prognosis. It does not have the same rate of transformation, anywhere near the same rate of transformation, and has been characterized by many clinicians as being totally distinct from myelodysplastic syndrome associated with exposure to

agents that can lead to the development of leukemia.
Q. What is the prognosis?
A. The prognosis is much better. The couple of studies that I have brought with me that discuss the relevant survival curves actually have been-- at the time of their publication were unable to make complete quantitative analysis, because the populations associated with 5q- syndrome didn't show-- basically their survival curves have flattened.
Q. What do you mean, they've flattened?
A. That, because of survival in the population, it was impossible to determine what the curves were, because those populations were still alive.
Q. Do you have an opinion as to her prognosis?
A. Only as it-- only as I have just related today with respect to what I can read in the literature as well as anyone else with respect to the life span of individuals with 5q- syndrome that have been studied. I have no personal opinion as to her current prognosis is.
Q. You don't plan on offering an opinion as to her prognosis?

A. No.
Q. What is the life span?
A. (No audible response.)
Q. Are you saying that it's not known what the-
A. The survival of patients with 5q- is demonstrably better than those associated with myelodysplasia as secondary to exposure to chemotherapeutic agents or where there are multiple chromosomal aberrations present.
Q. Okay. Secondary MDS patients with 5q-, what characteristics would they show that you claim this lady doesn't show?
A. They tend to present with a trilineage dysplasia, to begin with.
Q. So from the date that this disease is diagnosed-
A. Yes.
Q. -- or the day that the anemia first appears?
A. The anemia appears in the constellation of the disease. And there's not a great deal of time that transpires before you have the full-blown characteristics that are associated with it. It may even present with refractory anemia with excess

blasts.
Q. But the trilineage dysplasia presents at the same time?
A. Usually the multiple lineage involvement occurs before the anemia. You actually can find thrombocytopenia or lymphocytopenia early on.
Q. Are there studies of cases that that did not happen, that it happened after the refractory anemia?
A. I would not be at all surprised to find individual cases that present with any number of different variations. This is what it's my opinion you are most likely going to see in that population based upon what I have seen and read.
Q. Okay. What studies are you referring to with regard to that aspect of your opinion?
A. The myelodysplasia literature in general. Some of the Aksoy studies, Vigliani studies characterize the effects of benzene.
Q. Did you bring those with you?
A. Not all of them, no.
Q. Which of those did you bring with you that are relative to that aspect of your opinion?
A. This is going to take a little bit.

Q. If you want to name them by-- I think
that's the biggest problem.
A. Certainly the involvement of the
prevailing presentation of absolute lymphocytopenia
is referred to quantitatively in the Goldwater
article that I referred to.
Q. That was tab 3?
A. Yeah. That was probably the first
clinical characterization of that associated with
exposure to benzene. The myelodysplastic literature
in general related to secondary exposure to
chemotherapeutic agents. There are any number of
articles that I could point you to.
They're referenced in my book chapter,
in this article, but I didn't bring them all with
me. And the Kipen article refers again to the early
work by Greenburg. And it talks about print shop
workers with varying degrees of thrombocytopenia,
demonstrating the effect on platelets.
Q. Is that article included?
A. Yes. Certainly the references to the
first description of the 5q- syndrome disorder is
characterized by longstanding regenerative, slightly
macrocytic anemia that's a refractory anemia with
lower hemoglobin values-- I'm paraphrasing-- low to

normal lymphocyte count, and low to normal platelets.
Q. Which article was that?
A. That's number 12.
Q. Who is the author?
A. The author is Van Den Berghe, et al.
Another article by Van Den Berghe discusses some of the characteristics of 5q-, and separates them into two groups, one based upon simply 5q- as the sole anomaly, and the other with patients that present with that as well as additional chromosomal abnormalities, and characterizes differences between them. Platelet count is normal. Median granulocyte count is low normal.
Q. Which article is that?
A. It's another Van Den Berghe article.
It's number 13 in the series.
Q. Which page are you referring to?
A. Discussion begins on 192.
Q. Okay.
A. It actually characterizes a number of characteristics in the distribution within the population for blood cell count, platelets, granulocytes, red cells, and age distribution. It does discuss age. The median is sixty-six years.
I should tell you that I -pink the

clinical and morphologic findings and the pattern of findings is only a point with respect to distinguishing the 5q- syndrome from secondary myelodysplastic syndrome. I think the evolution of the disease, the prognosis, and the rate of transformation is far more important than whether a given individual presents with one finding first or another second. That can also be an artifact of when they're diagnosed in terms of the presentation of their disease.
Q. Certainly.
A. Again, white count lower normal, platelet count normal or elevated, by Sokal, et al. It's my number 14.
Q. Mrs. Lakie's platelet count was normal, wasn't it?
A. It was normal at the time of diagnosis.
Q. I'm sorry. Which article was that one you just mentioned?
A. Sokal was number-
Q. Sokal?
A. Yeah. It's number 14.
Q. Okay.
A. The Dewald paper as well-- it's number 16-- separates on the basis of prognosis and

progression patients with 5q- from patients that have multiple abnormalities or Sq- plus additional abnormalities.
Q. Describes a different prognosis and progression for those patients?
A. Yes.
Q. If they have more than one abnormality?
A. Yes. And the characteristics of the patients are different, too. Platelet count is much lower in those that have additional abnormalities. The macrocytic anemia, curiously enough, is higher in those that just have Sq- syndrome. Those are the only ones that I brought. Jandl's text also describes some differences, but it's not-
Q. Jandl?
A. Yes. It's a book chapter.
Q. In addition to what you've mentioned, what other factors do you consider to be important in distinguishing Sq- from secondary MDS?
A. The prognosis with respect to transformation is very significant.
Q. You mean it's quicker if it's secondary MDS?
A. It's also more likely to occur by

virtue of the order of magnitude, ten percent incidence of transformation in 5q-, and eighty to ninety incidence of transformation in secondary myelodysplastic syndrome. It's a huge difference.
Q. And did you bring your articles which indicate that ten percent transformation?
A. Those are included wit in the articles that I have discussed and that I brought today.
Q. And-
A. As a matter of fact, I think the Jandl book chapter summarizes it quite well. Patients having refractory anemia with excess blasts plus nonlobulated megakaryoctyes are at risk of transforming to AML, but the eventual incidence of AML, as I indicated, is well under ten percent.
Q. Do those same articles you've already cited also include or are those the articles which discuss the eighty to ninety transformation from secondary MDS to acute leukemia?
A. Some of them do. There are others, too, with respect to secondary myelodysplastic syndrome.
Q. Is that what you've brought with you today?
A. Not all of them have T_ brought with me

today. I did not bring all those with me. They are, however, cited in that, if not the book chapter brought.
Q. Tab 19 on the book chapter?
A. Yes.
Q. In addition to the presentation and the transformation to acute leukemia, are there any other distinguishing characteristics in your opinion?
A. The frequent presentation of other aberrations, the rate of the transformation.
Q. In addition to those?
A. We've already discussed the pattern, usually the pattern involvement of lineages of cells at the time of diagnosis. That's basically-- those are basically--
MR. WHITNEY: Did you mention the timing?
THE DEPONENT: We mentioned it earlier.
MR. WHITNEY: Oh.
A. The timing, you know, the timing is relatively-- for myelodysplastic syndrome that is secondary to bone marrow toxicity, the transformation not only occurs more-- with increased incidence, but it occurs within a matter of months to a year or so.

It's usually very quick.
Q. (BY MR. WILLIAMS) Are you talking about the transformation?
A. Yes.
Q. Is this included in the articles that you've discussed?
A. Yes.
Q. Other than the pattern, other than the transformation and the presentation, you mentioned a pattern of involvement of cell lineages?
A. Yeah.
Q. How would that be different in MDS, 5q-, and secondary MDS, 5q-?
A. Well, again, generally the same, as I said before. And, as I said, it's not a hard and fast rule, but in fact you do see more frequent involvement certainly following benzene. Lymphocytopenia is very frequent, absolute lymphocytopenia.
Q. We're talking about diagnostic criteria?
A. Yes.
Q. And, as you mentioned, the timing of the diagnosis plays a part in what factors are noted in a person's medical record, don't they

A. With respect to whether they present, that's true. It's conceivable that a person might not-- it is true. The timing is going to provide some artifact with respect to what you might see. But you have to keep in mind that the frequency of progression for 5q- syndrome is very, very small, whereas the frequency of progression for myelodysplastic syndrome is very, very high. And so timing is going to be a relatively small factor with respect to that. And it's not likely to confuse what you see in terms of characterization of diagnosis in the literature, because that progression is ultimately associated with terminal transformation or death associated with myelodysplastic syndrome. So survival is different as well.
Q. Would the lesion be different for secondary MDS, 5q-, and MDS, 5q-?
A. That is a very interesting question. At this point nobody knows. Janet Rowley at Chicago has a hypothesis that suggests that the lesion associated with 5q- secondary to exposure to chemotherapeutic agents involves the deletion of an undiscovered tumor suppressor gene somewhere within the 5q31 region or area. One could surmise that in fact that is the -- that is associated with a

different prognosis.
At this point in time, our approach is to characterize what's associated with altered function in cells that express the 5q-. So there are a number of different hypotheses that are put forward. Haplo insufficiency as a function of deletion of one of the chromosomes has been hypothesized.
I've included that in the model that I presented in that paper as a potential selection mechanism in the process. Whether that's distinct between 5q- syndrome and the involvement of secondary myelodysplastic syndrome I don't think is clear, but it certainly is a progression. If, in fact, it occurs, it must be because 5q minus has a very low rate of progression, incidence of progression.
There are a number of theories that have been put forward to suggest that there are, in fact, differences. At this point we do not have a clear picture of structurally what they are.
Q. So it's uncertain?
A. Yeah.
Q. At this time?
A. It's uncertain at this time. It's clear that there are differences in the prognosis, so

there must be something different about it. One of the characteristics that is most likely associated- that certainly is associated with it is the very high frequency of involvement of other chromosomes in secondary 5q- does occur.
Keep in mind, when we talk about the numbers and I present a study-- I present a summary of some of the studies in here that show the differences, the numbers, the index in here, you see involvement of 5, 7, 5q-, 7q-, or both, and you compare cross-studies for de novo versus secondary, there is a very, very high rate associated with secondary.
But, even in a study where you have a ninety-two percent incidence in secondary, you have to keep in mind that that only represents about a thirty percent involvement of 5, that 7 is involved forty to fifty percent of the time, and it's both of them together where you see such a high number. But 5 is involved to a lesser extent than 7, and certainly 5 by itself occurs to a lesser extent than any of the others in secondary.
Q. 5q- does occur by itself, though, in the secondary MDS leading to MDL?
A. To a certain extent, yes, it does.

Q. 5q- occurs by itself without any other cytogenetic abnormalities?
A. It can occur, yes, and has been described. But it's the less frequent presentation.
Q. Okay. Is there anything else in 5q syndrome that you distinguish from secondary MDS other than what we have been discussing?
A. Frequently association with benzene exposure at high levels, but that's-- that's intrinsic to the discussion we've had today.
Q. Well, both occur in conjunction with benzene exposure?
A. I do not believe 5q- syndrome has been associated with elevated benzene exposure. I certainly concur that secondary myelodysplastic syndrome is associated with benzene exposure.
Q. Give me your precise definition of 5q syndrome for purposes of your last statement.
A. 5q- syndrome is an idiopathic refractory anemia that's associated with primarily individuals of advancing ages, the median incidence probably on the order of the mid-sixties, between fifty and seventy or eighty. It tends to be associated with a macrocytic anemia, more frequent among women than men, and it has a relatively low

rate of transformation into acute myelogneous leukemia relative to other myelodysplastic syndromes.
Q. You're defining it as idiopathic, though, aren't you, which takes it out of the realm of being caused by-- possibly being caused by a-- I don't want to say mutant-
A. What I just gave you is a definition you can read from many sources with respect to what the 5q- syndrome is. When you see 5q- syndrome, which is a syndrome within that constellation of findings and in that particular group of individuals, you see it referred to as idiopathic.
Q. And 5q- has been defined since what time?
A. I included one of the earlier references-- I'm not sure it's the earliest, but I think it's very close to that-- as being described published in 1974. Myelodysplastic syndrome really wasn't recognized by the FAB, with a constellation of defined criteria for diagnosis, until 1983. I think it was 1983-- 1980, 1983.
Q. Haven't most of the epidemiological studies-- weren't they performed prior to the FAB classification and the articulation of the 5q syndrome?

A. Wel, not 5q- syndrome. Myelodysplastic syndrome, yes. And I referred to that earlier. That's one of the issues or problems in defining myelodysplastic syndrome that is associated with benzene exposure.
There are those, especially from an epidemiologic perspective, who would say that 5q- that myelodysplastic syndrome hasn't been associated with benzene exposure, but the preleukemia that's been described in the literature for years is consistent with myelodysplastic syndrome, as are the constellation of effects that are seen associated with chemotherapeutics in the evolution of AML, wherein you clearly have myelodysplastic syndrome as a precursor.
Q. And you know of no literature indicating cases of 5q- syndrome as being caused by benzene?
A. I don't believe-- I've told you I don't believe that 5q- syndrome is associated with benzene. I do think myelodysplastic syndrome as a secondary consequence of exposure to benzene occurs. Now, it can involve 5. I said that. But 5q syndrome is a separate entity.
Q. Well, defining it so that it cannot be

possibly caused by benzene-- let me rephrase the question.
Do you know whether or not the=a are cases describing patients with symptomatology similar to Ms. Lakie's that have been thought to have incurred their disease process from benzene exposure?
A. If you say "have been thought to," I would be safe in saying yes to just about anything having been published as a hypothesis if, in fact, and there are for a fact-- I don't know if I brought any-- discussions of individuals who present with a transient or persistent cytopenia involving one cell type that don't progress or go on to anything else. We don't have cytogenetics on them. Chances that they are, I think it's unlikely that we're looking at 5q- or in most of those, because the presentation doesn't look like that which you see in Sq- syndrome, but it's conceivable. What I'm saying is that the 5q syndrome that is seen as being described in these studies is a separate entity with a totally different prognosis than myelodysplastic syndrome, that there's no evidence to suggest that that's associated with benzene exposure.
Q. But are there cases of patients

presenting with the symptomatology that Ms. Lakie has presented with who have been considered to have acquired that disorder from benzene exposure or from chemical exposure?
A. If you say "symptomatology," and you're talking about a macrocytic anemia with lineage involvement and one or more cell types, that clearly has been associated with benzene exposure. Now, whether or not it involves 5q-, there is absolutely no basis on which to speculate, because cytogenetics have not been associated with those earlier studies. And, as a matter of fact, you can probably call into question some of the morphologic characteristics, because we're talking about techniques and diagnoses that are not within the rubric of the FAB or anything in the context of how differential diagnosis is done today.
Q. Other than the fact that the cytogenetics were not available for some of these studies, the patients would present with symptomatology which would closely parallel Ms. Lakie's; is that correct?
A. Symptomatology that roughly parallels Ms. Lakie's. Ms. Lakie's symptomatology closely parallels and, in fact, is consonant with what has

been described in the literature with respect to the 5q- syndrome. That's not what is associated with exposure to benzene as described in the literature as generally being associated with benzene exposure.
Q. But there have been patients in the literature which have had her symptomatology which have been thought to have acquired that from benzene exposure?
A. As I said, the general symptomatology associated with bone marrow suppression has been associated with benzene exposure.
Q. Okay. Were there any other distinguishing characteristics you wanted to articulate?
A. I think we've probably exhausted the subject.
Q. So that would be the extent of the basis for your opinion that 5q- syndrome is not caused by benzene exposure?
A. Essentially, yes.
Q. Okay. I want to ask you a couple of questions about your report, which should be in the front of Exhibit 3. Do you plan on offering an opinion as to the amount of benzene that was absorbed by Ms. Lakie, or are you going to assume for purposes

of your opinion that a hundred percent was absorbed?
MR. WHITNEY: It all depends on how you phrase the question to him.
A. I believe the most likely scenario that describes the available concentration of benzene that could be absorbed is that Dr. Jacobus has presented. Of all the descriptions I've seen, that one, I think, is the most cogent and likely. Now, having said that, I am going to assume absorption within the context of that model.
Q. (BY MR. WILLIAMS) Dr. Jacobus?
A. Yes. Now, by the same token, I'm fully prepared to offer the same opinion based upon the assumption that all the benzene that you could possibly extract or pound out of that product was absorbed. So the worst case does not present-- as we've said earlier, is not going to change my opinion.
Q. Does the model which Dr. Jacobus has erected, has that been subject to peer review?
A. As it relates to this particular study, no.
Q. Okay. You know whether it's ever been used before by anyone for any purpose?
A. Precisely for this purpose, no. I'm

not aware of that.
Q. Is his physiological model that h`
constructed been used, if you know, by any other
scientist for any purpose?
A. Similar physiologic models are used all
the time to evaluate the potential for absorption of
drugs from the stomach, from the gut, and from
elsewhere that bear-- individual components of this
model are used all the time. Whether they've been
put together precisely for the purpose at hand I'm
not aware.
This is a very case specific issue.
The methodology and assumptions he made in
constructing his model I have seen many times. And
you can find it in classic textbooks on
pharmacokinetics, pharmacodynamics, and
pharmaceuticals.
Q. The models that he's constructed?
A. Components of them, components of the
model, the assumptions and the techniques.
Q. Which book would you refer me to for
those assumptions?
A. Any number of different textbooks
discuss issues related to the issue.
Q. Can you name an authoritative text on

the subject?
A. I COU7 d name several. The old Goldstein and Aranow text, which has now got a separate set of authors, discusses various aspects of this. Any text on pharmacology is going to discuss absorption.
Q. What is the Goldstein book? Is that not pharmacology?
A. It's Pharmacological Bases of Drug Disposition, I think. I'm not certain. I could get you the reference, but I don't have it at my fingertips. The principal issues in there are predicated on very well understood concepts.
Q. Any other text other than that one?
A. There are several. If you'd like, I can provide you with those, but I can't do it as I sit here right now.
Q. Okay. I would like. Doesn't have to be a lot. One or two.
You are not a pharmacologist, are you?
A. My training is essentially that of a pharmacologist. I would consider that I'm a pharmacologist in many aspects. It depends on your definition of pharmacology. I trained in the department of pharmacology and toxicology.

Q. Your pharmacology was part of- your toxicology training, wasn't it?
A. Yes.
Q. Okay.
A. I have the same training a pharmacologist has, and then additional training in toxicology.
Q. You went to school to get a degree in toxicology?
A. Yes. And pharmacologists, certainly at the University of Rochester, took a portion of the curriculum of toxicology. That's what they took. So I took everything a pharmacologist took, plus additional material.
Q. This was at Rochester?
A. Yes. You find the same at Colorado, too, just about anywhere.
Q. Do you hold yourself out as an expert in pharmacology?
A. Some aspects of pharmacology, yes.
Q. Have you ever been qualified to testify in court as an expert in pharmacology?
A. I believe I probably have been qualified as an pharmacologist, slash, toxicologist on occasion. I believe I have, yes.

Q. And that specific term has been used in addition to toxicology?
A. I think so.
Q. Can you tell me the case where that occurred?
A. Not specifically, no. The concepts are the same.
Q. Concepts of toxicology and pharmacology?
A. The concepts relating to absorption, distribution, dose are the same.
Q. You're not board certified in pharmacology, though, I take it?
A. There are no boards in pharmacology.
Q. I want to ask you about your estimates of benzene release, and that's page 3 of your report. I want to find out how you came out with a figure using Jacobus's numbers. You came out with an absorption figure of forty-six to a hundred and seven micrograms a day, down toward the bottom of the paragraph?
A. Yes.
Q. Take me through your analysis; tell me how you got to that.
A. I believe I took it straight from Mr.

Jacobus's summary.
Q. Your understanding is that that's what is his?
A. I believe so. That's my best recollection.
Q. Okay. Well, let's just go quickly through the figures you have here. Up at the top you give three amounts for oral, stomach, and intestine absorption?
A. Yes.
Q. What did you do with those figures? Did you add them together?
A. I believe I took the-- based upon residence times, I took-- I believe I bracketed them. I believe that's what I did. And, as I recall, I went through and checked them. I took the residence times versus the amount of the variation in residence times that was realistic versus the amount that was released in the conditions of his analysis and bracketed those.
Q. I don't understand what that means.
A. The residence times would vary to some extent. There's a range. So I took the absolute amount that was released as a function or the-right-- as a function of the conditions, and then

calculated based upon differences in the range of residence times that material would spend in each compartment.
Q. Are those calculations indicated here?
A. No. They're in his report.
Q. Okay. So the first line of figures, oral, one fifty-two micrograms a day, is that the bracketed figure you came up with?
A. For varying residence times, yes.
Q. Okay. What I'm trying to find out is how you got down to forty-six to one hundred seven micrograms a day.
A. I think, if you look at Dr. Jacobus's report, that that's the range that he gives.
Q. You say that this range that he gave assumes a certain amount of Orafix Special used?
A. I'd have to go back and look at it.
Q. You don't recall?
A. I don't recall today. Obviously, yes. It does. I know it does. It's implicit in his design. But I don't know what it was.
Q. So these things are all from his report?
A. I believe they are.
Q. Did you apply-- you then have a fifty

percent rate of absorption via the oral mucosa you've assumed?
A. I assumed a fifty percent rate via the oral mucosa. Now, that's an assumption. The skin is clearly much less, and the stomach or intestine is much more. And so I base that on the fact that it is epithelial tissue. I expect it to be higher than skin but lower than the gut.
Q. You expect it to be absorbed through the oral mucosa?
A. There would be some absorption through the oral mucosa.
Q. The fifty percent rate means fifty percent of the benzene in the product?
A. No. Fifty percent of the benzene in the solution will be absorbed by the oral mucosa.
Q. Are you assuming-- you mean saliva solution?
A. Yes.
Q. Are you assuming fifty percent of what Dr. Jacobus found was bioavailable would be absorbed in the oral mucosa?
A. Yes.
Q. Okay. Then you added those, that amount?

A. Yes.
Q. To the amount absorbed in the stomach?
A. And the amount that you would expect to be absorbed in the intestine. You come up with a range.
Q. You didn't indicate what that amount was here in your paragraph?
A. No. I-- basically I used those to determine--
Q. Did you do calculations?
A. Yes.
Q. Do you have your notes?
A. No, I don't.
Q. Where would those be?
A. I'm not sure.
Q. Did you do any draft reports?
A. No.
Q. In this case?
A. No.
Q. Was it the same amount of exposure you came up with in the Petry case?
A. I think it's based upon a similar calculation and modeling by Dr. Jacobus. I think it's comparable. Certainly, if the numbers weren't exactly the same, it's very close.

Q. Did you retain your worksheets on these calculations?
A. No.
Q. Those wouldn't be on computer somewhere?
A. No.
Q. In the last paragraph, your conclusions-- I believe you've already gone through most of this-- in your opinion you say, "It is my opinion, to a reasonable degree of scientific certainty, that there is no reliable evidence to suggest that the plaintiff's purported exposure to the available benzene in Orafix Special was sufficient to cause or contribute to the development of her disease."
Reliable evidence, are you referring to the materials you brought here in your notebook, which is Exhibit 3?
A. Yes. As well as other data in the epidemiologic and toxocologic literature that relate to benzene. We discussed some of those today.
Q. And some of those would be summarized in your-
A. Some of them. Some of the issues and some quest=-ns. For instance, you have raised the

Infante study, which I have not provided. And there are other more recent studies that also look at the levels of benzene associated with exposure to adverse health effects. I have provided several.
Q. What does the Infante study indicate with regard to this deposition?
A. It doesn't indicate anything. It assumes a level of exposure that I don't believe is defensible, and certainly hasn't been corroborated by anyone else.
Q. You disagree with Infante's conclusions?
A. I disagree with his assumptions, and I disagree with his conclusions based upon these assumptions.
Q. Which article are you referring to, the Pliofilm study?
A. Certainly the risk analysis associated with the Pliofilm study, based upon the assumed exposure study, which has been repeatedly criticized. I brought several articles today that characterize exposure in that same population and found it to be much higher.
Q. Are those in your book?
A. Yes.

Q. Which one of these?
A. The Kipen articles.
Q. Kipin and Goldstein?
A. And Goldstein, Wong, Paxton. There's several others, but those are the ones that I brought. But, again, even the Rinsky study doesn't provide material evidence that the levels we're talking about here are associated with an adverse effects.
Q. Rinsky was doing a mortality study, wasn't he, studying humans?
A. Yes.
Q. I don't have, for some reason, a complete copy of your CV. I wanted to ask you some questions about it. Do you need to look at it, or can I use yours?
A. Well, depends how difficult this gets whether I need to see it or not.
Q. Hold onto it. I may not need to go past page 1. I don't know.
You've been at University of Colorado since '89?
A. Yes.
Q. Is that your primary employer?
A. Yes.

Q. What is the bulk of your professional time since '89? What has it been spent doing?
A. Research, teaching, directing a training program in toxicology, serving as leader of the Cancer Causation Program for the University of Colorado Cancer Center, and serving as a member of the Department of Pathology in the School of Medicine.
Q. Of these three, was the bulk of your time mostly spent with the Molecular and Environmental Center?
A. Yes, I would say.
Q. How much of your time?
A. It varies from year to year. It can vary, generally-- teaching can vary-dramatically, anywhere from twenty to forty percent.
Q. Teaching in what department?
A. Teaching across the board, whether it's in the Department of Occupational Medicine, Pathology.
Q. Okay.
A. Research can vary, usually between thirty and forty percent.
Q. The remaining percent?
A. Yeah. Fifteen percent service.

Q. What does that mean?
A. That's consultation.
Q. For litigation?
A. Some of it's litigation. Some of it is drug development. Some of it is advisory to the government.
Q. Who have you consulted with on drug development?
A. Several companies.
Q. Which ones?
A. Oh, Hoffmann-La Roche, Merck, DuPont-Merck, Puget-Salva (phonetic). There are others. Sandoz. Sandoz is another one.
Q. How much of your time is spent in litigation, doing litigation consultation?
A. It varies from year to year. Last year, about fifteen percent, was probably split.
Q. Between-
A. It was probably slightly more pharmaceutical than litigation. Pharmaceutical development, safety evaluation was probably about fifty and some percent. The year before that litigation was higher.
Q. What percentage of your income comes from litigation work?

A. Last year it would have been about probably a third, slightly less.
Q. How about in '94?
A. It was probably close= to forty percent, maybe higher. I'm not sure exactly.
Q. You know for '93?
A. No. It was probably higher in '93.
Q. But not by fifty percent?
A. It probably was close to fifty percent.
Q. And how about '92?
A. It would have been about the same. We're getting down into rarefied numbers. I don't remember exactly.
Q. Is it income separate from your income from the University?
A. Yes.
Q. Is your consulting income also separate?
1.9 A. All of it.
Q. I'm sorry. Consulting with drug companies, separate?
A. Yes.
Q. Do you also do consulting with the American Petroleum industry?
A. I do consulting on safety evaluation

and risk assessment for a variety of people from time to time that would include companies within the American Petroleum Industry. I have consulted from time to time on small projects relating to bases for risk assessment for the American Petroleum Institute. I also do the same for regulatory agencies.
Q. How long have you done consulting for the American Petroleum Institute?
A. Probably, on and off, since 1989. I'm not sure I consulted with them in 1989.
Q. And does that include consultation with petroleum companies?
A. On issues related to, separate and distinct from litigation, I'm including them all in the same category, yes.
Q. Oh, you're including this in litigation?
A. No.
Q. Oh, okay. Separate from litigation have you consulted-- what petroleum companies have you consulted with?
A. Exxon, American Petroleum Institute, Amoco. That may be it.
Q. What chemical manufacturers have you

consulted with?
A. I think that basically it is in terms of issues that relate to safety evaluation or regulations.
Q. Well, are there any other issues you've consulted with them on other than litigation?
A. Not that I recall.
Q. Okay. Do you know what percentage of your income has come from consulting with the American Petroleum Institute or any of those companies?
A. I'd be surprised if it's one percent.
Q. Is that fairly consistent over the-
A. Yeah. It's a very low number. My consultation with Exxon is recent, and that may represent the slightly higher number. It might be on the order of a few percent.
Q. That's for '95?
A. I believe so, yes.
Q. What number are we talking about?
A. What do you mean?
Q. What amount of money are we talking about?
A. I won't divulge my income. It's on the order of a few percent of my total income, probably

less than that.
Q. Okay. How about for litigation, what amount are we talking about for '95?
A. '95, as I said, was probably on the order of a third. Probably between thirty and forty, thirty-five percent, something like that.
Q. Of what number are we talking about?
A. Thirty to thirty-five percent, that would be my total income.
Q. No, in numerical, not percentage, what amount of money are we talking about?
A. No. I won't divulge my income. Under contract I am prohibited from discussing my salary and income by the University. I'm talking about the total percent of my income. I'd be happy to discuss that with you in context.
Q. The University prevents you from saying how much money you make from cases?
A. Yes. If, in divulging to you the amount I make from cases, I give you the percentage, you can determine my salary, I am prohibited from doing that.
Q. You have a contract that says that?
A. Yes.
Q. What's the purpose of that?

A. It's a peccadillo of the administration. I do not know why.
Q. Can you furnish a copy of the contract provision?
A. I am not sure I can do that.
Q. Why not?
A. Because basically the provisions of that contract or that specific contract are confidential. I have signed an agreement to that effect. I can tell you precisely what the individual provisions are without discussing figures. I've given you some of it here with respect to the distribution of my income.
Q. I don't want to know figures with respect to this issue. I'm interested in contractual prohibitions.
A. I am prohibited from discussing my salary and income, as outlined in my letter of appointment, which I have agreed to and signed.
Q. Would that also include if a court ordered you to divulge your income?
A. Yes.
Q. If the court ordered you, you have to, don't you?
MR. WHITNEY: What's your point? We

have a discovery meeting. We'll address it the:-
It's getting close to my witching hour now.
Q. (BY MR. WILLIAMS) Have you ever been
forced to disclose that income in any other case?
A. No.
Q. Have you ever received any grants from
the API?
A. Yes.
Q. When was that?
A. I've had a grant from the API since
1989.
Q. Since 1989?
A. Yes.
Q. What is that grant for?
A. For research looking at proving of the
biological basis of risk assessments associated with
leukemia, leukemogenesis.
Q. What is the amount of the grant?
A. I think my direct costs this year are
on the order of a hundred and seventy thousand.
Q. What does that mean?
A. That means that that's the amount that
I see for research purposes after indirect costs and
other features or factors are taken out.
Q. That's after cost?

A. That's the cost. That's what I see.
That's what I see.
Q. When you say "you see," is that paid to
you directly?
A. No. It's paid to me as a principal
investigator at the University of Colorado.
Q. Okay.
A. There are other studies that are part
of that, and there are indirect costs that the
University exacts.
Q. I guess it is a hundred and seventy
thousand dollar figure we're talking about, 1995?
A. '96. '95 would have been about the same.
Q. And that's an amount that you see after
your costs have been paid for?
A. No, not after my costs have been paid
for. That's what I see. That's what I have to use
for research purposes.
Q. You see a hundred and seventy thousand?
A. Yes.
Q. Okay. And has that been constant since
'89, or has it been higher?
A. It's been roughly constant. I think
one year there was a slight difference of maybe
thirty thousand dollars. There might have been a

fluctuation.
Q. Down or up?
A. Up.
Q. So one year it was two hundred thousand?
A. Close, yes.
Q. In other years it's been around one seventy?
A. Yes.
Q. Have you received any grants from the CMA?
A. Yes. I've had approximately four years of funding from the CMA.
Q. Four years through this year?
A. Pardon?
Q. Four years through this year?
A. Through last year. Again, my direct- my direct costs were on the order of fifty thousand.
Q. Per year?
A. Per year.
Q. What has that grant been for?
A. That grant was for characterizing the mechanisms of thymic lymphoma in mice associated with butadiene exposure.
Q. Any benzene?

A. No.
Q. Just butadiene?
A. Just butadiene.
Q. Have you received any other grants
other than those?
A. Oh, yeah. I have grants from the
National Institutes of Health to look at mechanisms
of chemically and drug-induced leukemogenesis. That
is in its third year. The direct costs are on the
order of two hundred thousand dollars a year.
I had a five-year grant with National
Aeronautic and Space Administration to look at
adverse health effects on the immune and hemapoietic
system associated with space flight and potential
exposure to toxic substances.
Q. How much was that grant?
A. It varied. It was on the order-- it
was from sixty to a hundred thousand dollars a year,
direct. I'm giving you direct so that you can
compare them.
Some of these things have strange-
indirect figures are different. That's University
contract.
I've had small grants from the National
Cancer Institute to do specific studies related to

their China study. That's probably on the order of twenty thousand dollars total.
Q. A year or for the whole thing?
A. Twenty thousand total at this point. We probably will be doing some additional studies with them as well.
Q. Who was that grant from?
A. National Cancer Institute.
Q. Okay.
A. I've had various-- I've had grants from pharmaceutical companies to look at issues related to drug development. I've done studies on DDC for Hoffmann-La Roche. I think that was for two years. I think that was two years at a hundred thousand a year, but may have been a year and a half.
Q. When did that end?
A. 1995, beginning of '95. I've got several studies pending, several grant proposals pending, both with NIH as well as pharmaceutical companies. So my funding base changes dynamically, and it is hard to predict from one time to the next, depending on what's funded and what isn't.
Q. Any proposals pending with SmithKline Beecham?
A. No.

Q. Any proposals pending with a-;
companies, subsidiaries or associate companies of
SmithKline Beecham?
A. Not to my knowledge. I'm not -familiar
with what companies are subsidiaries of SmithKline
Beecham, but I certainly don't think that they're -- I
have no studies pending with anybody that ells in
that category.
MR. WILLIAMS: Can we take a
one-minute break?
(Whereupon, at 4:29 p.m., a recess was
taken.)
Q. (BY MR. WILLIAMS) I just want to go
over a couple of things in your education. After you
graduated from college, it says here in '68-
A. Uh-huh.
Q. -- you got a degree in chemistry. You
worked at the General Hospital; how do you pronounce
that?
A. San Joaquin.
Q. San Joaquin?
A. Uh-huh.
Q. And did you get a degree as a medical
technician there?
A. I got a certification as a medical

technologist.
Q. You got a certification?
A. Yeah.
Q. How long was that program?
A. Program was a year to a year-and-a-half I believe.
Q. And you took courses while you were working there?
A. I took courses as part of my training, and additional courses in diagnostic hematology.
Q. And what courses in diagnostic hematology did you take
A. Basically laboratory hematology at University of San Francisco, University of California, San Francisco.
Q. Was that one course?
A. It was several. I think there were three or four.
Q. Three or four courses?
A. Yes.
Q. How long did that last?
A. They were part of the process that was over the same course of time.
Q. Okay. Who supervises medical technicians in a hospital?

A. It depends on the state. Depends on the particular jurisdiction and the laws. California, I'm licensed as a clinical laboratory scientist, which by, I think, current law means that I'm qualified to direct a laboratory. Some states require a physician to direct a laboratory. Other states don't. It varies.
Q. So California allows toxicologists to do that?
A. No. It requires a licensed and clinical laboratory scientist.
Q. What do medical technicians do?
A. A medical technician, which is not what we're talking about, is someone who performs specific laboratory tests at the direction of a technologist or a laboratory director.
Q. What are we talking about-- I'm sorry- MT?
A. Is medical technologist.
Q. Medical technologist?
A. Yes.
Q. What does a medical technologist do?
A. It is an individual who performs laboratory-- diagnostic laboratory tests in a clinical laboratory. That ranges from chemistry,

hematology, radiology, urinalysis, bacteriology, etc., etc.
Q. Is that done at the direction of a physician?
A. In some cases. In other cases not. Depends on-- as I said, depends on the specific conditions of the state. The variation in regulations that pertain to laboratory-- clinical laboratories is quite large in the United States. There are some states that require no certification.
Q. And California allows medical technologists to run a lab and conduct experiments?
A. This has nothing to do with experimentation. It is performance of clinical laboratory tests. It has nothing to do with experimentation.
MR. WHITNEY: Okay. You answered the question.
Q. (BY MR. WILLIAMS) Have you ever run a lab performing clinical laboratory tests?
A. Supervised laboratory clinical tests in New York during my training in toxicology for part of that time, and I practiced as a medical technologist prior to that in California for a brief period of time.

Q. Before you went to New York?
A. Right.
Q. Other than that period of time, have you ever?
A. I directed a clinical laboratory involved in support of chronic toxicity testing at CIIT, but that's not involved in clinical testing.
Q. What type of clinical testing did you do in New York?
A. Hematology, primary hematology.
Q. Can you be more specific?
A. Routine laboratory testing involving blood counts, peripheral blood, morphologic analysis of bone marrow, bone marrow smears.
Q. Was this part of your training in the University? No?
A. No. That was independent. That was independent.
Q. And what was your title? Was it medical technologist?
A. I don't have any idea what my title was.
Q. Where was the lab? What lab were you working for?
A. Strong Memorial Hospital.

Q. Okay. I don't see that on here.
Okay. Let me see your CV. I imagine it will be on there, won't it?
A. What?
Q. Strong Memorial Hospital?
A. Yeah, but not in that context. My training in pathology is, but basically we're talking about what I did during the summers and at various times for spending money. I don't list it as a-
Q. As a job experience?
A. Yeah.
Q. Okay. Were you working under the direction of a physician?
A. No. No.
Q. Were you working under the direction of anyone?
A. I was working under the direction of the supervisor of the overall laboratory. I don't remember the details. I was working primarily emergency and triage. So I was working odd hours and pretty much by myself.
Q. Was t~ supervisor a physician?
A. No.
Q. What were his qualifications or her qualificati3ns?

A. She was a medical technologist.
Probably had a master's degree. As I recall, she had
a master's degree.
Q. In medical technology?
A. Yes.
Q. Okay. After you finished the medical
technology program, did you apply to law school-- I
mean-- I'm sorry-- medical school?
A. I applied to graduate schools and
medical schools.
Q. And when was this?
A. Over the same period of time, at the
end of my training in medical technology.
Q. Did you get into medical school-
A. I was accepted at-- yes.
Q. Did you get into medical school the
first time you applied?
MR. WHITNEY: Objection. Now really.
Come on now. This is getting kind of ridiculous.
THE DEPONENT: What do you mean, the
first time? I applied. You mean the first year I
applied?
MR. WILLIAMS: Yeah.
A. I don't believe so. I think it was the
second year.

Q. (BY MR. WILLIAMS) How many schools did you apply to the first year?
MR. WHITNEY: Objection.
A. I don't remember. Several.
Q. (BY MR. WILLIAMS) Several?
A. Several.
Q. And this would have been after-- when did you first apply?
MR. WHITNEY: Objection. Let's get some relevant questions, okay, if you have some.
MR. WILLIAMS: These are relevant.
A. I don't recall.
Q. (BY MR. WILLIAMS) Was it after the first year you got out of college?
A. Yes.
Q. And so you didn't get in, and then the second year, the year after that, you applied to medical school again?
A. It was after. As I said, it was a year after college. That's when I was in medical technology. That's when I first applied. And I believe I applied one round, and then I came back and applied again.
Q. Okay. And you say you got in that time?

A. Yes.
Q. Where did you get in? Where were you accepted?
A. University of California, San Francisco.
Q. And you did not go to medical school there?
A. No. I was already at Rochester when I got their letter.
Q. You had one year in the University School of Medicine. Were you accepted in the School of Medicine?
A. Yeah. I took courses in both School of Medicine and toxicology program for a number of years. In fact, I was still taking medical courses at the-- when I began the fellowship in pathology.
Q. Were you auditing these courses or taking them for credit?
A. Taking for credit.
Q. Were they part of your toxicology program?
A. No.
Q. Were you actually accepted in the School of Medicine degree program?
A. At the point at which I needed to enter

the clinical portion of the program, I left Rochester and went to North Carolina.
Q . To worst?
A. Yes.
Q. At CIIT?
A. Yes.
Q. So your testimony is you were accepted into medical school at the University of Rochester with a degree program?
A. I was enrolled in courses of the School of Medicine. I did not finish the program. I did not enter the formal medical program at the point at which I had to take a degree in medicine.
Q. Did you ever actually apply to medical school at the University of Rochester?
A. As part of matriculating and the courses that I took, yes.
Q. But in terms of the degree in medicine?
A. The M.D./Ph.D. program at Rochester incorporated and assimilated students from the graduate program in the M.D. program at various times during the history of the program. I matriculated in the program for a number of years and took courses in medicine. I did not elect to formally enter the clinical years and take a degree in medicine.

Whether or not that would have been-- whether I would have had that opportunity at that time I don't know.
I elected not to.
Q. You elected not to apply?
A. I elected not to finish, and that would have required applying to the program.
Q. To the medical school program?
A. Yes.
Q. In a traditional four-year medical school program, when does the clinical aspect of it start? Is it the third and fourth year?
A. Year three and four.
Q. Did you take all the courses that would have been required of a medical school student in the first and second years of their academic program?
A. The vast majority of them.
Q. Do you recall which ones you took?
MR. WHITNEY: Objection.
A. The vast majority. It would probably be easier to tell you the ones I didn't take.
Q. (BY MR. WILLIAMS) What didn't you take?
A. I didn't take psychiatry.
Q. Is that the only one?
A. I believe so.
Q. Did you take anatomy?

A. Yes.
Q. Did you complete the course in anatomy?
A. I didn't complete neuroanatomy.
Q. Go ahead. I'm sorry.
A. I didn't complete neuroanatomy.
Q. Is that a second-year course?
A. Neuro courses are the second year courses-- neuropathology, neuroanatomy, and a number of other things. I took the neuropathology, but I didn't take the rest of it.
Q. When you had postgraduate training as part of pathology at Strong Memorial Hospital, what did this entail?
A. Gross pathology, anatomic pathology, some surgical pathology, hematopathology, as well as research.
Q. The ones you just listed were the courses you took?
A. They weren't courses. I was basically serving as a fellow, reviewing cases, evaluating material, participating in autopsies, reviewing surgical specimens.
Q. Who were you working with during this training? Did you have a-
A. A mentor?

Q. Yes.
A. Eric Schenk was a mentor. J.C.K. Lee was also a mentor.
Q. And they're both pathologists?
A. Yes.
Q. Do you consider yourself to be an expert in pathology?
A. Experimental pathology, yes. I am a member of the-- what is now the American Association of Investigative Pathology, formerly the American Association of Pathologists. Yes. I have a full professorship in the Department of Pathology in the School of Medicine at the University of Colorado.
Q. And you teach experimental pathology?
A. I teach pathology both to graduate students and medical students.
Q. Have you been qualified in court to testify as an expert in pathology?
A. As an experimental pathologist, yes.
Q. Tell me what an experimental pathologist is as opposed to an anatomical or clinical pathologist.
A. An experimental pathologist is an individual who basically studies mechanisms and pathogenesis of disease, and structural alterations

associated with disease, very similar to what we're talking about in terms of pathogenesis of leukemia. Whether you say I'm a hematological pathologist or an experimental pathologist or experimental hematologist, I think they all basically relate to the same type of expertise and activity.
Q. How is that different from an anatomic and/or clinical pathologist?
A. Anatomic pathology is that branch of pathology that deals primarily with either the analysis of histology or gross pathology associated with disease processes.
I'm not an M.D. I'm not a clinician. I do have expertise in both of those areas. I have reviewed and performed studies as a pathologist, but I am not a pathologist and do not specifically diagnose disease except in the context of providing expert opinion on differential diagnosis of hematological diseases when requested to by a physician.
Q. Did you mention clinical pathology?
A. Clinical pathology deals with the clinical laboratory diagnosis and the use of clinical laboratory procedures in the support of clinical diagnosis.

Q. So you don't consider you=self an expert in those areas of pathology; you consider yourself an expert in experimental?
A. I'm certainly an expert in clinical pathology as it relates to the differential diagnosis of hematological diseases, and I'm licensed to perform those particular types of tests in California. I serve as a consultant on occasion in differential diagnosis of leukemias.
The diagnosis of leukemia has changed dramatically over the course of the last several decades, two decades in particular. Clinical diagnosis does not usually provide a great deal of information. It provides some. But the differential diagnosis of leukemia types is primarily a laboratory related activity at this stage.
Q. You're not board certified in pathology I take it?
A. No, I am not.
Q. You have an associate fellowship listed here in The National Society of Experimental Hematology?
A. Yes.
Q. What's involved in becoming a member of that society?

A. You have to be elected by the membership based upon your research activities and publications in the field.
Q. Where are they based?
A. I don't know. I'd have to tell you.
Q. I take it then, to be a member of the American Association of Pathologists, you don't have to be an M.D.?
A. No. But you have to be elected.
Q. Is it the same process, you're elected by the membership?
A. Yes.
Q. Do you get someone to sponsor you for that thing? Is that how it works?
A. No. There's a membership committee that usually evaluates your credentials, and that's the way most professional societies work that require that. They have specific requirements with respect to education, training and/or publication experience. And then, when that's reviewed by a committee, the committee usually makes recommendations to the membership. And that's the way it's usually done.
Q. How many members does the International Society of Experimental Hematology have? Do you know?

A. Maybe-- I suspect it's on the order of one or two thousand.
Q. How about the American Association of Pathology?
A. That's a much larger organization. I couldn't tell you exactly. That information is readily available.
Q. Okay. Have you been asked to review any of the plaintiff's experts' opinions in this case?
MR. WHITNEY: If he's asked to provide a rebuttal opinion, I'll let you know. Right now he's not.
Q. (BY MR. WILLIAMS) Okay. But have you been asked to review their opinions?
A. Specifically, no. I've been asked to review their reports and their depositions with respect to formulating my own opinion, but I haven't been asked to render an opinion specifically relating to theirs.
Q. So, as of today, you have no plan to state a rebuttal opinion to the-
A. If called upon to do so, I will. I have not been called upon to do so.
Q. Have you formulated any rebut=al

opinions at this point?
MR. WHITNEY: He's my witness, and if he's asked to, I'll tell you.
MR. WILLIAMS: Well, are you going to let me take his deposition again?
A. In general, it is clear or should be clear that my opinion differs substantially from opinions that have been offered by experts for the plaintiffs in this case. I could go through and itemize several specific points and why I disagree with each of them. I have not been asked to do so. I think it's obvious that my opinions are different, and that I differ with the opinions that they've offered.
Q. (BY MR. WILLIAMS) Obviously. Other than with respect to what you've stated today and in your report, are there any other opinions in addition to those that you have in response to the deposition testimony you read from the plaintiff's experts or their reports?
A. At this point in time I believe that they have all been covered within the context of my opinions as offered in this case.
Q. Do you have any other opinions in this case thus far that you have not covered yet?

A. No.
Q. You say you've been asked to consult in differential diagnosis in clinical settings?
A. On occasion, yes.
Q. Have any of those cases involved myelodysplastic syndrome?
A. Probably, yes. I can't recall specifically an individual case, but that's almost certainly a yes.
Q. Why is that almost certainly a yes?
A. Because myelodysplastic syndrome is one of the common abnormalities that's encountered in a clinical setting relating to diseases of the blood.
Q. Are you called upon to consult because of your research, the research you've done in the field of benzene toxicity?
A. I'm called upon I think in part because of that and in part because of my general research on mechanisms of leukeogenesis, and in part because of my knowledge of experimental hematology, and in part because of my expertise in morphologic diagnosis and idiopathic diseases of the blood. All of those are- they're all related, and they're all expertise that I have, and expertise that I use either in research or on issues that are related to differential

diagnosis.
Differential diagnosis represents a relatively small pa=z. of what I do. It is not a routine part of my activities anymore.
Q. When was the last one you did?
A. I believe I probably-- I believe it was in the fall or winter of 1995.
Q. Was that with Dr. Heron (phonetic) in Denver?
A. I don't remember. I don't recall who the physician was that was involved. I believe I was asked in the context of confirming information, laboratory information that was already available on the patient.
Q. Obviously you were asked by the doctor?
A. Yes.
Q. How many of these differential diagnosis consultations do you think you have been involved in? You say that's not very frequent?
A. Not anymore. I mean usually it's in the context of hemopathology rounds. On occasion it's a specific patient. It's not a routine activity that I participate in anymore.
At Rochester, I used to do it much more often in the context of morphologic diagnosis of bone

marrows. That was a long time ago. And my-- I have no-- no clinical responsibilities or laboratory responsibilities in the clinical laboratory at Colorado.
Q. So, since '89, how many do you think you've done, just one or two or-
A. Half a dozen maybe.
Q. Did you do any while you were at CIIT?
A. Rarely. I think maybe once when I was at CIIT I did.
Q. So the most would have been when you were at Rochester in the pathology fellowship?
A. Yes.
Q. That was back in '74 to '76?
A. Yes.
Q. Were you ever asked to consult with any patients with 5q- syndrome?
A. I don't believe so.
Q. And you've never examined or treated any patients with any kind of disease, have you?
A. For purposes of this discussion, no. When I was at Rochester, I did examine patients in the context of clinical activities that I was involved in. That was when I was training.
Q. Right. And you were not involved in

the treatment of those patients?
A. No.
MR. WILLIAMS: Let me just take a second to go through.
(Whereupon, there was discussion outside the record.)
MR. WILLIAMS: That's all I have.
(**Whereupon, at 5:00 p.m., the deposition concluded.)**